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A MANUAL OF MEDICINE

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A

Manual of Medicine

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MEDICAL DEPARTMENT OF THE ROYAL NAVY

VOL. II.

GENERAL DISEASES—CONTINUED

DISEASES CAUSED BY PARASITES

DISEASES DETERMINED BY POISONS INTRODUCED INTO THE BODY

PRIMARY PERVERSIONS OF GENERAL NUTRITION

DISEASES OF THE BLOOD

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A MANUAL OF MEDICINE



DISEASES CAUSED BY PARASITES

Definition and classification.—The term parasite is applied to any living organism, whether animal or vegetable, which in some stage of its life-history or throughout its existence derives its nourishment wholly or in part from other living organisms. This definition includes not only those parasites (*e.g.* *Trichina*) which obtain their food from the tissues of their hosts (true *parasites*) but also those (*e.g.* *Tænia*) which feed upon the food materials prepared by their hosts (*Commensals*); but it excludes those which, living within or upon the body of some other organism, assist in the preparation of food substances, which they share with the host, the two living together for mutual advantage (*Symbiotics*). The definition includes all those, such as fleas, mosquitoes, etc., which temporarily alight upon the surface of the host (*Ectoparasites*).

Parasites may be classed into vegetable or *PHYTOPARASITES* and animal or *ZOOPARASITES*.

The latter belong, in the main, to three well-marked zoological groups—CESTODA or Tape-worms and Bladder-worms, TREMATODA or Fluke-worms, and NEMATODA or Round-worms and Thread-worms. There are other human Zooparasites of less importance, and the whole may be classed as follows:—

ZOOPARASITES

Phylum **Protozoa.**

Class RHIZOPODA.

Order LOBOSA—*Amæba*.

Class MASTIGOPHORA.

Order FLAGELLATA—*Trichomonas vaginalis*.

Class SPOROZOA.

Order GREGARINIDEA—*Gregarina*.

Order COCCIDIDEA—*Coccidium oviforme*, some *psorosperms*.

Order MYXOSPORIDEA — Some *psorosperms*; probably *Hæmatozoon* or *Plasmodium malariae* belongs to this Order.

Order SARCOCYSTIDEA—*Sarcocystis*, or Rainey's Corpuscles in muscle fibres.

Class INFUSORIA.

Order CILIATA—*Paramœcium coli*.

Phylum **Platyhelminia**.

Class TREMATODA—*Fasciola hepatica*, *Distoma crassum*, *D. sinense*, *D. lanceolatum*, *D. conjunctum*, *D. ophthalmobium*, *Amphistoma hominis*, *Bilharzia hæmatobia*, and others.

Class CESTODA—*Tæniæ solium*, *T. saginata*, *Bothriocephalus latus*, *T. tenella*, *T. lophosoma*, *T. elliptica* or *cucumerina*, *T. nana*, *T. madagascariensis*, *B. cristatus*, *T. echinococcus hominis*, and others rarely met with.

Phylum **Nemathelminia**.

Class NEMATODA—*Ascaris lumbricoides*, *A. mystax*, *Oxyuris vermicularis*, *Trichocephalus dispar*, *Filaria sanguinis hominis*, including the doubtful species *F. Bancrofti* and *nocturna*, *F. perstans*, *F. diurna*, *F. loa*, and others, *Dracunculus medinensis*, *Dochmius* or *Ankylostoma duodenale*, *Trichina spiralis*, *Anguillula stercoralis*, *Strongylus bronchialis*, *Eustrongylus gigas*, and other less common species.

Class ACANTHOCEPHALA—*Echinorhynchus gigas*.

Phylum **Annulata**.

Class HIRUDINEA—*Hirudo medicinalis*.

Phylum **Arthropoda**.

Class INSECTA—*Cæstrus hominis*, *Pulex irritans*, *P. penetrans* or *Chigæ*, *Pediculus capitis*, *P. vestimenti*, *P. inguinalis*, *Anopheles claviger*, *A. pictus*, and other ectoparasites.

Class ARACHNIDA—*Sarcoptes scabiei* (the itch insect), *Demodex folliculorum*, *Pentastoma tænioides*, *P. constrictum*, *Leptus autumnalis* (the harvest bug).

Class CRUSTACEA—*Gammarus pulex*, which has been recorded as parasitic on man in one or two instances.

PHYTOPARASITES

Group **Thallophyta.**

Class FUNGI.

Sub-Class SCHIZOMYCETES—Various species of *Micrococcus*, *Macrococcus*, *Streptococcus*, *Staphylococcus*, *Bacterium*, *Bacillus*, *Spirillum*, etc., which are associated with various infectious diseases; *Streptococcus actinomyces* (the ray fungus of actinomycosis), *Sarcina ventriculi*.

Sub-Class BLASTOMYCETES or SACCHAROMYCETES—*Saccharomyces cerevisia*, *S. neoformans*, associated (whether accidentally or causally is uncertain) with carcinomatous and sarcomatous growths; *Monilia candida* of thrush.

Sub-Class ZYGOMYCETES — *Mucor mucedo*, a saprophyte capable of becoming a facultative parasite in rarer forms of mycosis.

Sub-Class ASCOMYCETES—*Aspergillus fumigatus*, *A. flavescens*, both of which species are facultative parasites in aspergillar mycosis; *Penicillium glaucum*—a facultative parasite in rarer forms of mycosis; *Achorion Schoenleini* of tinea favosa or favus; *A. keratophagus* of onychomycosis; *Trichophyton tonsurans* of ringworm or tinea tonsurans, including the varieties *T. Microsporon Audouini*, *T. megalosporon endothrix*, *T. megalosporon ectothrix*; *Microsporon furfur* of chloasma or pityriasis versicolor.

The exact botanical position of the last four of these parasites is still doubtful, for although in the disposition of their hyphæ and production of spores they resemble the lower Ascomycetes, the sexual reproduction followed by the formation of ascospores characteristic of this sub-class has not been observed in these parasites. There has also been much doubt as to the identity of the fungus of thrush. It was at one time thought to be the same as *Oidium lactis*, and more recently as *Saccharomyces mycoderma*.

From the clinical point of view these two groups of parasites exhibit marked differences, for whereas the ill effects on their host produced by the animal forms are mainly due to the appropriation of the nutriment, to mechanical irritation and inflammation, or in a few cases to loss of blood from wounds inflicted by them, the results of the invasion of most of the vegetable organisms are rather of a toxic character, in this way determining the specific infective diseases.

ANIMAL PARASITES

PSOROSPERMS

These are minute parasitic Protozoa belonging to the class SPOROZOA, which includes the *Gregarinidea*, *Coccididea*, *Myxosporidea*, and *Sarcocystidea*. All are parasitic and multiply by spore formation, and most of them are intracellular. The term "Psorosperm" has been rather loosely applied to the spores and spore capsules formed by members of the last three subdivisions, and some of the intracellular structures thus designated are not parasites at all. A good example is the *Coccidium oviforme* of the rabbit's liver, which is found also in epithelial cells of the skin, mucous membranes, and bile duct of man. It occurs in the liver, as small nodules which contain the encysted parasites and their spores, either free or within the enlarged and altered epithelial cells, in various stages of development—(a) small oval bodies with clear refractive capsules, having sharp double contours, containing uniformly granular protoplasm; (b) oval capsules with the protoplasm shrunk into a central nucleated sphere; (c) the central sphere divided into four rounded spores; (d) the spores rather oval in shape, and composed of a membrane enclosing falciform young; (e) the capsules dehisce and liberate the spores, which develop into minute amœbiform bodies.

The Myxosporidea are amœboid when mature, become encysted and break up into "psorosperms," and the Sarcocystidea are very common in the muscle fibres of various animals, where they produce spores with falciform young, and are sometimes called *Rainey's corpuscles*.

Some interest has been attached to these organisms by the assertion, now disproved, that they were responsible for the formation of cancer growths (see p. 138).

PARAMÆCIUM

The *Paramæcium coli*, which is stated to be an almost constant parasite in the pig, occurring in the cæcum and colon, is not infrequently found in the like situation in the human subject, associated with diarrhœa. A unique case has been recorded (*Tr. Path. Soc. Lond.* 1899) in which the organism was discovered in the liver of a patient who died of malignant disease of the stomach, occupying the interior of numerous small cysts connected with the bile ducts. Apparently the parasites had reached the liver *viâ* the common bile duct, and setting up irritation had led to the formation of cysts—a condition similar to the invasion of the rabbit's liver by "psorosperms."

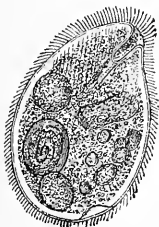


FIG. 1. — *Balantidium coli*, or *Paramæcium coli*. (After Malmsten. $\times 300$ Diams.)

TREMATODA

The Trematoda or fluke-worms have generally a flat, leaf-like body, devoid of segmentation. They adhere to their hosts by one or two or many suckers, and as a rule have no hooks. They have a mouth and digestive sac, but generally no anus. With the exception of *Bilharzia hæmatobia*, they are hermaphrodite. There is no body cavity, the viscera being surrounded by a general parenchyma of connective tissue cells, covered by muscle layers, epidermis, and chitinous cuticle. The excretory system consists of longitudinal canals opening to the exterior through a contractile vesicle, generally placed posteriorly, and there are finer canals, given off from the main ones and ending in "flame cells." Some of the Trematoda develop directly, without the intervention of a second host, but others have a complicated life-history and require two hosts for their completion. In the latter case, the general history is similar to that of *FASCIOLA HEPATICA*, which is only occasionally found in man, but is very common in the sheep. The mature fluke inhabits the liver and bile ducts, and produces ova which are discharged. These develop free swimming *ciliated embryos* in pond water. The embryos attach themselves to the bodies of pond snails (*Limnæa truncatula*) and bore into them, there becoming quiescent *sporocysts*. By internal gemmation, these develop a number of *rediae*, which may by budding produce others. The *rediae* eventually give rise by internal gemmation to a brood of *cercariæ*, which leave the body of the water snail and become encysted upon some water-weed, grass, water-cress, etc., and only develop into mature flukes when taken into the alimentary canal of the sheep or man. The following flukes occur occasionally as human parasites—(1) *FASCIOLA HEPATICA*; (2) *DISTOMA CRASSUM* or *BUSKII* (intermediate host, probably marine shellfish); (3) *DISTOMA SINENSE*, occurring in the liver and bile ducts, in man in China; (4) *DISTOMA LANCEOLATUM* (intermediate host, probably pond snails, as for *Fasciola hepatica*); (5) *DISTOMA CONJUNCTUM*, occasionally found in man in China and India; (6) *AMPHISTOMA HOMINIS*, found in the cæcum and colon of man in India and Assam; (7) *DISTOMA OPHTHALMOBIUM*, a very small fluke found in the human eye; (8) *DISTOMA RINGERI*, found chiefly in the lungs of inhabitants of Japan and Formosa, of the usual fluke shape, one-third to half an inch in length, and covered with very small spines; (9) *BILHARZIA HÆMATOBIA*. This Trematode is remarkable as having the sexes separate. The male is cylindrical, about half an inch long, and has two suckers, whilst the female is narrow and filiform and longer than the male, and is lodged in a narrow but deep *gynæcophoric canal* or groove on the ventral surface of the male during copulation. The suckers of the female are small. There is a mouth, a bifurcated intestinal sac, but no anus. It inhabits the blood-vessels—portal vein,

mesenteric veins and vessels of the bladder and rectum—of man in Egypt, the Cape, and other parts of Africa, as well as Mesopotamia, and gives rise to endemic hæmaturia. The ova have a transparent, brown-coloured shell, which is pear-shaped, or oval and pointed at one end, where there is a terminal or lateral projecting spine, and are discharged in the urine of the affected individual. When fully formed, the ova are about $\frac{1}{160}$ inch in length, and $\frac{1}{300}$ inch in transverse diameter. Development up to the formation of the characteristic *ciliated larvæ* takes place within the egg membrane, and specimens

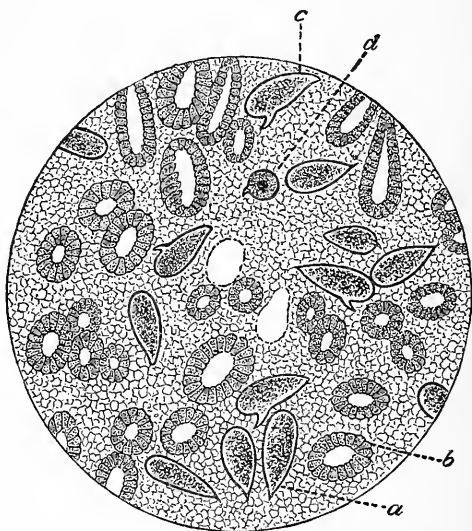


FIG. 2.—Section from rectal mucous membrane from a case of Bilharzia disease. *a*, normal ovum; *b*, section of a follicle; *c*, ovum with lateral spine; *d*, laterally spined ovum seen in transverse section. (After Sonsino.)

from the urine may exhibit all stages from undivided yolk or mulberry cleavage mass up to the fully-formed ciliated larva. When ready to be liberated the larva presents a conical anterior end and terminal oval papilla, from which there radiate several ciliated ridges ending in a ciliated ring surrounding the base of the cone. The posterior part is narrower and uniformly ciliated. The egg-shell bursts by a characteristic longitudinal slit, extending about two-thirds of its length, and the empty shells may also be found in the urine. The subsequent fate of the larvæ is unknown, but it is probable that they enter some intermediate host and go through a development similar to that of *Fasciola hepatica*, and that the parasite is taken in by man in the form of an

encysted cercaria in water or adherent to vegetable matter. There is also some reason to believe that infection may take place by the embryos penetrating the skin or entering the anus or urethra during bathing, and this has been regarded as explaining the far greater frequency of the affection in males than females, as the latter much less frequently enter the water.

Symptoms caused by Trematoda. — Disease arising from fluke-worms is a rare occurrence in this country, but it is not uncommon in China, Japan, and India, where it is brought about by *Distoma crassum*, *D. sinense*, and *D. conjunctum*. The parasites mainly inhabit the liver, bile ducts, and duodenum, and the symptoms they produce are necessarily determined by their number and exact habitat. For the most part the symptoms are anæmia or wasting with indigestion, headache, nausea or vomiting, diarrhœa with pale stools, or containing mucus or blood. In severe cases there are signs of extensive hepatic disease, with enlargement and tenderness, jaundice, ascites, and febrile symptoms. The diagnosis is not easy, but may be greatly assisted by examination of the stools for any evidence of the flukes or their ova. In Japan the disease is often fatal.

Amphistoma hominis is associated with severe or fatal choleraic symptoms.

The invasion of the lungs by the *Distoma Ringeri* leads to a frequent hæmoptysis, which may become so severe as to cause grave anæmia and even death. The parasite penetrates the lung substance, and discharges its ova with the rusty blood-stained sputum, thus affording the most reliable diagnostic evidence. Hitherto treatment of this condition has been ineffectual.

The symptoms produced by the ova of *Bilharzia hæmatobia*, for the adult worm is practically harmless, are mainly hæmaturia, with frequent and painful micturition, or diarrhœa with tenesmus and discharge of blood-stained mucus, according to the bladder or rectum being the seat of the affection. The spined ova which are discharged into the smaller blood-vessels of these organs pass into the tissues of the submucosa and mucosa, finally escaping into the cavity of the viscus, and being subsequently voided. The irritation set up by the passage of these bodies causes inflammation and bleeding, and in course of time a chronic cystitis or proctitis, with considerable hypertrophy of the muscular coat, and thickening and polypoid growths of the mucous membrane. In course of time other organs, such as the prostate, vesiculæ seminales, and kidneys may become involved.

All degrees of symptoms are exhibited, from the mere occasional passage of a little blood without pain or discomfort to severe suffering and a progressive anæmia terminating in death. Vesical calculus, with the ova for a nucleus, is of frequent occurrence. The discovery of the characteristic ova or empty egg-shells in the discharge will determine the diagnosis, and a microscopical examination of the urine and stools should never be neglected.

Treatment.—No means are known of killing the parent worms and hence cure is impossible, and treatment must be directed to alleviation of symptoms.

CESTODA

TÆNIA SOLIUM

This worm has the form of a jointed ribbon attached at one end, where it is very narrow, to the intestinal wall, the remainder hanging freely in the intestine. It may reach the length of several yards. At its attached end there is a small rounded head or *scolex*, having a diameter of $\frac{1}{40}$ inch, or about the size of a small pin's head; behind the

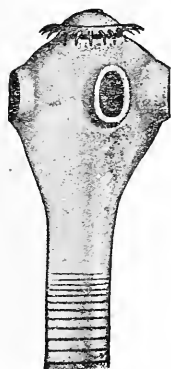


FIG. 3.—Head of *Tænia solium*, magnified.
(After Leuckart.)

scolex follows the short narrow *neck*, and the rest of the worm, which may include 800 to 850 segments, is called the *strobila*. The scolex is roughly pear-shaped, with a rounded prominence called the *rostellum*, around the base of which is a double row of slightly-curved, pointed, chitinous *hooks*. The rostellum is capable of retraction, and the position of the hooks varies somewhat in consequence; when fully expanded their free ends are rotated backwards; when retracted the points of the hooks are directed forwards. Behind the circlet of hooks there are four circular cup-shaped *suckers*, whose margins project somewhat from the surface of the scolex. In the head, particularly in the region of the hooks round the base of the rostellum, are a number of dark pigment granules. The strobila is made up of segments, or *proglottides*, in all stages of development. Near the scolex they are very short and narrow, and gradually increase in size towards the middle and posterior parts. Throughout, the proglottides are flattened dorso-ventrally; the anterior ones are broader than long, gradually becoming longer as we pass backwards, until the posterior ones are two or three times as long as broad. At the free end they are more loosely attached to each other than elsewhere, and they eventually become detached and expelled with the fæces of the host. The proglottides are constantly being added to

by gemmation from the scolex, so that, in reality, the strobila consists of a chain of developing gemmæ in all stages of growth, becoming finally mature at the posterior end. Upon one border of each proglottis, sometimes right, sometimes left, is the *genital papilla*, where is found the opening of the *genital pit*, in which both male and female ducts terminate. Minute examination of living and stained specimens, and of sections, shows that there is no trace of an alimentary canal or body cavity, but that there are rudiments of excretory and nervous systems with a complete set of hermaphrodite genital organs in various stages of maturity in each proglottis, the whole enclosed in a parenchyma of connective tissue cells, covered by longitudinal and circular muscle layers, and bounded at the surface by a layer of epidermal cells covered by a chitinous cuticle.

The *nervous system* consists of a pair of ganglia in the scolex, united by a transverse commissure, of two longitudinal nerves passing backwards through all the proglottides, and of slender nerves from the ganglia to the suckers.

The *excretory organs* include four main trunks, two along each lateral margin, running the entire length of the strobila. These are connected together in the scolex by a ring-like vessel, and, in the posterior part of each proglottis, by a straight transverse commissural vessel. Posteriorly, the main longi-

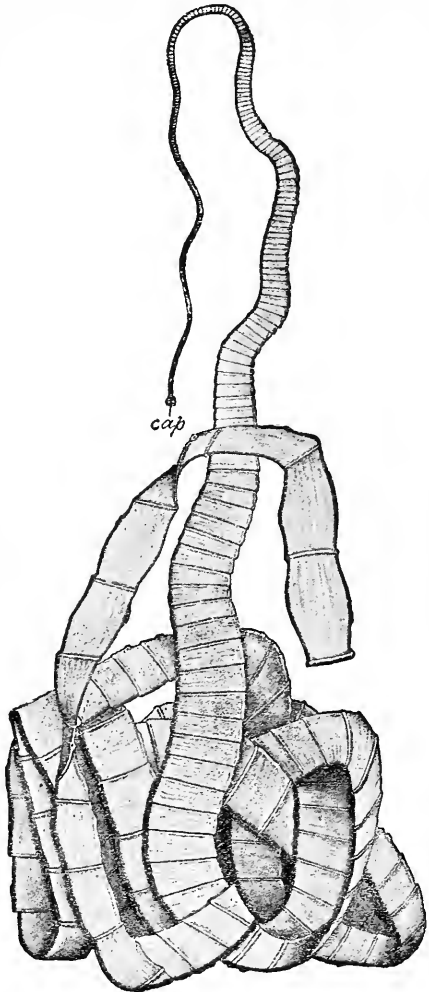


FIG. 4.—*Tania solium*. Entire specimen, reduced cap. head. (After Leuckart.)

tudinal trunks end in a pulsating *caudal vesicle*, which communicates with the exterior. Very fine canals are everywhere given off from the main trunks, and end in peculiar characteristic *flame cells*.

The *reproductive organs* begin to be formed at about the 200th proglottis, the male organs developing first, the female appearing further

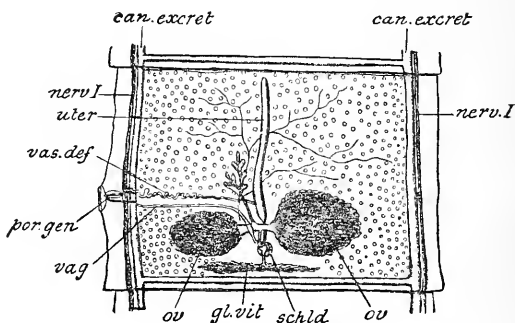


FIG. 5.—A proglottis of *Tania solium* with mature reproductive apparatus. *can. excret.* longitudinal excretory canals with transverse connecting vessels; *gl. vit.* vitelline glands; *nerv. l.* longitudinal nerves; *ov. ov.* ovaries; *por. gen.* genital pore; *schild.* shell glands; *uter.* uterus; *vag.* vagina; *vas. def.* vas deferens. The numerous small round bodies are the lobes of the testes. (After Leuckart.)

back. The male organs include the testes, made up of a number of rounded lobes scattered throughout the proglottis. Each lobe has a fine efferent duct, and ducts of adjacent lobes unite into larger ducts, and these, joining each other, eventually form a vas deferens, which is a convoluted tube extending towards the genital pit. Near its termination the vas deferens traverses an eversible cirrus or penis, enclosed at its base in a flask-shaped cirrus-sac. The female organs consist of a pair of ovaries situated at the posterior part of the proglottis, a pair of oviducts which unite into one and pass into a vagina, which leads to the external orifice. There is a yolk gland and yolk duct, which traverses a rounded shell gland as it runs forward to open into the oviduct. The uterus opens into the oviduct near the yolk duct, and there is a receptaculum seminis, to store the seminal fluid, opening into the beginning of the vagina. The uterus, in the youngest proglottis which has one, is a simple cylindrical diverticulum of the oviduct, and retains this character as far back as the 600th proglottis, where it begins to become irregularly branched.

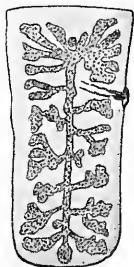


FIG. 6.—“Ripe” proglottis of *Tania solium*. (After Leuckart.)

The spermatozoa pass along the vagina to the receptaculum seminis, being derived from the same proglottis; and as the ova ripen they are

fertilised in the oviduct, become surrounded with food yolk from the yolk gland, and enclosed in a shell secreted by the shell gland. They then pass into the uterus and accumulate, this organ becoming gradually branched and distended with them. Thus the most posterior proglottides consist mainly of the much branched uterus full of spherical ova, the rest of the genital organs disappearing. The ova have very

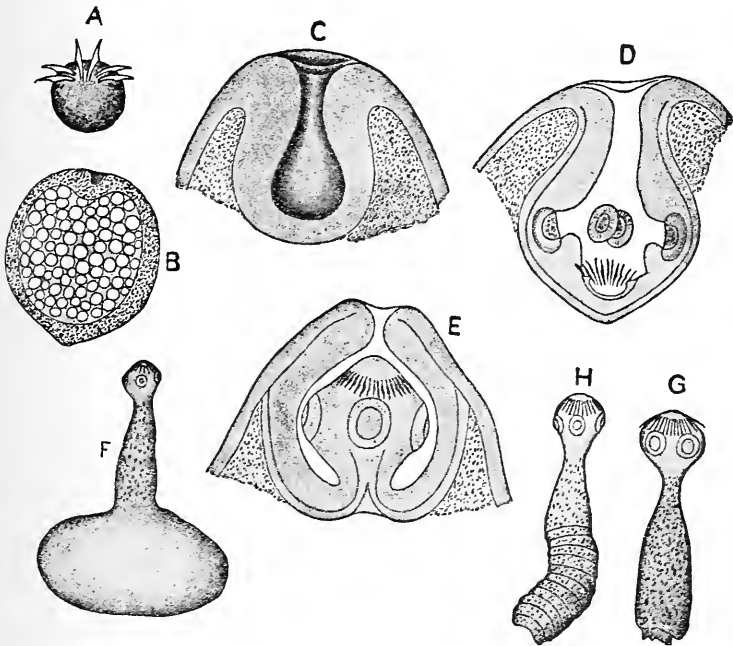


FIG. 7.—Development of Tapeworm. *A*, hexacanth embryo; *B*, Proscolex of *Tania saginata*; *C*—*E*, stages in the formation of the scolex of the same; *C*, the invagination before the hooks and suckers have become developed; *D*, after the appearance of the hooks and suckers; *E*, partly evaginated; *F*, fully evaginated scolex of *T. solium* with caudal vesicle; *G*, scolex of *T. serrata* with remains of the vesicle; *H*, young tapeworm of *T. serrata*. (After Leuckart.)

thick brown envelopes which exhibit characteristic radiating and concentric lines, the whole having a diameter of about $\frac{1}{100}$ inch.

Development.—The ripe proglottides having become detached and discharged, the ova in the uteri first develop into *six-hooked embryos* still enclosed in the egg membrane. If the proglottides or the escaped eggs should now be taken into the body of a pig, which, in the case of *T. solium*, is the ordinary intermediate host, the six-hooked embryos are liberated by the solution of the egg-capsule, and bore

through the wall of the alimentary canal, and are carried to the voluntary muscles or other organs, and, increasing in size, become rounded cysts filled with fluid. A single proglottis may contain as many as 50,000 eggs, so that an enormous number of such cysts may be produced in the tissues of a pig by the taking of a single segment into its stomach. This is known as the *prosclex stage*. An invagination appears on one side of the prosclex cyst, and on the inner side of this the four pit-like suckers and circlet of hooks characteristic of the scolex of the adult develop. When fully formed these are everted, and the rest of the embryo, becoming further dilated, forms a large bladder. This is the bladder-worm or *Cysticercus stage*, and is the common "measle" of pork or *Cysticercus cellulosæ*. The proper wall of the cysticercus, which is thin and semi-transparent, is often invested by a capsule formed around it from the connective tissues of the host. The cysticercus varies in size from that of a small pea to that of a marble, having an average diameter of $\frac{1}{6}$ inch. In order that any further development may occur, it is necessary that the flesh of a pig infected with *Cysticercus cellulosæ* should be taken into the alimentary canal of man. This, of course, can only occur if the flesh has been improperly cooked. The bladder is then disintegrated, the scolex attaches itself to the mucous membrane of the intestine, and by gemmation produces proglottides and passes into the adult or *strobila stage*.

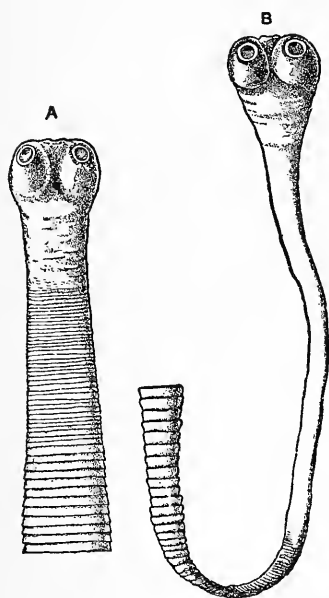


FIG. 8.—Head of *Tænia mediocanellata* or *saginata*. (After Leuckart.) A, retracted; B extended.

TÆNIA SAGINATA OR MEDIO-CANELLATA

This tape-worm occurs in man quite as frequently as *T. solium*, and it has the same general structure. It differs, however, from *T. solium* in the following characters:—(a) It

Although it is the strobila stage of *T. solium* which is most commonly met with in man, yet occasionally the *Cysticercus cellulosæ* is found, man playing the part of the intermediate host. Cases of *Cysticercus* occurring in the subcutaneous and intermuscular tissue, and in the brain, eye, substance of the heart, etc., have been placed on record.

may attain a greater length, varying from 15 to 23 feet, and is made up of more proglottides, sometimes over 1000; (b) the mature proglottides are longer and broader; (c) the scolex is larger (about $\frac{1}{25}$ inch) and has four large circular pigmented suckers, but no rostellum or circling of hooks, hence it is sometimes called the "unarmed tape-worm"; (d) the uteri of the ripe proglottides have more branches, which are narrower and more slender; (e) the ova are oval in outline, not spherical, having a long diameter of $\frac{1}{700}$ inch and a short one of about $\frac{1}{850}$ inch.

Owing to the absence of hooks its attachment to the intestine is less firm than in the case of *T. solium*, and the worm is therefore more commonly expelled whole.

In its development *T. saginata* resembles *T. solium*, but the intermediate host is not the pig, but the ox, and the *Cysticercus* (*Cysticercus bovis*) is rather smaller than *Cysticercus cellulosæ*. *T. saginata* is often called the "beef tape-worm," whilst *T. solium* is spoken of as the "pork tape-worm," since man becomes infected by eating imperfectly cooked "measled" beef or pork, as the case may be.

BOTHRIOCEPHALUS LATUS

This tape-worm is not commonly met with in this country, but sometimes occurs in Ireland. It is found in Switzerland, Russia, Poland, and other European countries. It is the largest and longest of the human tape-worms, being often 8 or 9 yards long, and nearly an inch in width, and may have as many as 4000 proglottides. The scolex is oval, bluntly pointed, or club-shaped, has two lateral longitudinal slit-like suckers, and is without hooks. The head measures about $\frac{1}{25}$ inch in width, and about $\frac{1}{10}$ inch long. The proglottides are very numerous, the anterior immature ones being very narrow. In the mature proglottides the genital pores are ventral (not marginal), the male orifice in front

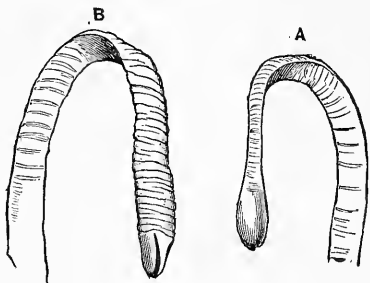


FIG. 9.—Head of *Bothriocephalus latus*. $\times 8$.
A, from the flat side; B, from the margin.
(Leuckart.)

of the female. The uterus is a single tube, regularly folded, so as to form an opaque central rosette, of a brown colour, owing to pigmentation of the shells of the contained ova. Unlike the *Tæniæ*, the ova do not mature in the uterus, but leaving the proglottides early, are expelled with the fæces of the host. They are larger than the ova of *T. solium*, and have an oval form, with a firm, thick shell which opens by a lid or

operculum to allow the embryos to escape. They measure about $\frac{1}{3\frac{1}{2}0}$ inch in length, and $\frac{1}{3\frac{1}{2}0}$ inch in width. Ciliated larvæ are soon liberated when the ova become immersed in water, and these subsequently develop into six-hooked embryos and become Cysticerci in the pike and other fresh-water fish.

OTHER TAPE-WORMS OF MAN.—Rarely, other species of tape-worm occur in man, viz.: T. TENELLA, which is a small tape-worm, whose corresponding Cysticercus is found in the sheep (CYSTICERCUS OVIS), T. LOPHOSOMA, T. ELLIPTICA, BOTHRIOCEPHALUS CRISTATUS, and others.

Symptoms caused by the Cestoda.—The symptoms arising from the presence of *adult tape-worms* in the intestine are generally indefinite and trivial. The parasite frequently exists in the alimentary canal for some time without giving rise to any inconvenience whatever, and often are wholly unsuspected until a foot or two of tape-worm or a few proglottides are passed *per anum*. On the other hand, symptoms of more or less importance have been attributed to tape-worms, or at any rate have coincided with the presence of the parasites, and have disappeared after they have been expelled by treatment. These symptoms are mainly due to local irritation, or constitutional disturbance, or are phenomena of a reflex nature. Symptoms suggestive of local irritation include abdominal uneasiness or actual griping pain, nausea, or vomiting, furred tongue, foul breath, slight diarrhoea alternating with constipation and capricious or inordinate appetite. Among the symptoms indicating constitutional disturbance are wasting or emaciation, anæmia, a sense of languor or debility, with fretfulness and depression, and pains in the limbs. The evidences of reflex disturbance are giddiness, twitching of muscles or convulsions, or even choreiform, hysterical, epileptiform, or maniacal attacks. More or less anæmia, headache, and vertigo are not by any means infrequent symptoms, and it may be said, in general, that the constitutional and reflex disturbance is more marked in delicate and weakly subjects, or in those with a highly sensitive nervous system. The anæmia consequent on the presence of the Bothriocephalus is frequently most severe and even fatal, and it has been supposed that some special toxic substances are produced by this worm.

The symptoms produced by *Cysticercus cellulosæ* are necessarily very variable, and depend upon the tissues and organs affected, and upon the number of the cysts present. If only a few cysts are developed in the subcutaneous or intermuscular tissues, they will give rise to no inconvenience whatever, but, if numerous, they may

produce painful subcutaneous tumours, or by affecting the inter-muscular tissues may cause muscular pains and general weakness of the limbs. When they affect the brain or other parts of the central nervous system obscure nervous symptoms, indicating irritation or pressure, but necessarily varying with the part affected, are present. Many of the recorded cases of *Cysticercus* in the brain had severe epileptiform convulsions, with general mental disturbance. There is, however, nothing diagnostic, and generally the presence of a *Cysticercus* is wholly unsuspected until revealed *post-mortem*. Several cases of the occurrence of a *Cysticercus* in the vitreous body of the eye are recorded—a condition to be detected by the ophthalmoscope.

Treatment.—A number of anthelmintic remedies have been recommended, such as kousso followed by a purge, areca nut, oil of turpentine, kamala powder, the bark of pomegranate root, and crushed pumpkin seeds, but there is no doubt that the best remedy is male fern. This should be employed as follows:—Give the patient liquid food only for a day, then administer a full dose of castor-oil in the evening, and next morning, if the oil has acted, a draught containing $\mathfrak{z}\text{i}$. to $\mathfrak{z}\text{iss}$. of liquid extract of male fern. This may be followed in a few hours by a second smaller dose of castor-oil. The object is to clear the intestine, and so expose the worm to the poisonous action of the male fern. The stools should be examined to discover if possible that the head of the worm has been expelled, and a cure effected.

To prevent infection with tape-worms care should be taken that all pork or beef, even if unsuspected, is sufficiently cooked to destroy any possible *Cysticerci*. They are killed by a temperature of 170° F., and prolonged exposure to cold or prolonged immersion in brine will also destroy them. Attention should also be given by sanitary authorities to the inspection of meat, and no measled pork or beef should be passed for food. The measles are easily detected by the naked eye, and when cut into the vesicles are found to be filled with a milky-looking albuminous fluid, and there is a dense white spot at one point on the inside of the vesicles. In both pigs and oxen, the tongue, diaphragm, and superficial muscles of the neck, shoulder, loin, and hip are the most usual situations affected. It is important also that all tape-worms and their segments from infected patients should be destroyed by heat so as to prevent the spread of the parasites.

ECHINOCOCCUS HOMINIS (*Hydatid*)

This is the most serious of the Cestodes parasitic in man, for, unlike the others, it is not a commensal living in the intestine, but it migrates from the alimentary canal into various organs, where it forms larger or smaller cysts. In the case of other human Cestodes, the parasite is generally the adult strobila, whilst *Echinococcus* is the *Cysticercus* stage of a tape-worm found in its adult state in the dog and wolf viz. : *Tænia echinococcus*.

The mature worm, as found in the dog's intestine, consists of a scolex and a strobila made up of three proglottides only. In length it is seldom more than one-fourth of an inch. The scolex possesses a rostellum, with a double circlet of about thirty hooks and four suckers. There are two excretory canals opening posteriorly, and the terminal proglottis is much larger than the others, having a lateral genital pore and a set of hermaphrodite genital organs. The ova, when transferred to another suitable host, *e.g.* man, give rise to six-hooked embryos, which bore through the intestinal wall and are carried in the blood to a suitable resting place, *e.g.* liver or lung, where they become encysted and metamorphosed into the hydatid.

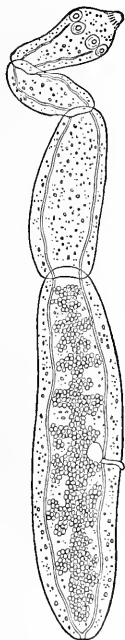


FIG. 10.—*Tænia echinococcus*. (After Cobbold.)

THE HYDATID.—The very young hydatid is spherical, and is surrounded by a spurious capsule of fibrous tissue formed by irritation of the surrounding organs of the host. As the hydatid grows the irritation which it sets up increases and the spurious capsule may attain a great thickness, and generally becomes very vascular. Within the capsule is a thick, transparent, elastic membrane, having a beautiful concentric lamination, called the *cuticular layer* or *ectocyst*, enclosing a central granular mass. This mass subsequently forms a layer of cells on the inner surface of the cuticle, known as the *granular layer* or *endocyst*, and a cavity containing a clear colourless limpid fluid forms. The ectocyst is composed of chitin, and when taken from the fibrous capsule and cut into has a peculiar tremulous motion and coils on itself along its cut margins,

whilst the endocyst is delicate and thin, and is the vital part of the parasite. The fluid is characteristic, colourless, transparent and clear, or occasionally slightly opalescent, having a low sp. gr., and containing a large quantity of common salt, but no albumen. Sometimes no further development, beyond increase in size, occurs, but most

commonly secondary or *daughter cysts* are developed by gemmation from the cellular granular membrane, either exogenously or endogenously, most commonly the latter. These are the brood capsules, and give rise to several *scolex heads*, attached by short pedicels to the granular walls of the cysts. The daughter cysts are often so numerous as to completely fill the cavity of the original mother cyst with which their walls are continuous. The daughter cyst walls have the same structure as the cellular endocyst of the parent cyst, but have an *internal* lining of chitinous cuticle similar to the parent ectocyst. Thus the layers of the daughter cyst wall are the reverse in position to those of the parent cyst, a fact which is explained by Leuckart on the supposition that the daughter cysts are really modified scolex buds and that they grow originally from the external surface of the hydatid, and subsequently become invaginated, so that the outer membrane becomes internal. Instead of forming daughter cysts, the endocyst may, and

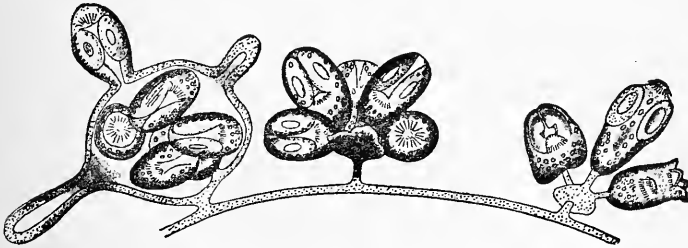


FIG. 11.—Cyst of *Tania echinococcus* with the developing daughter cysts and scolices.
(After Leuckart.)

often does, give rise directly to scolices either singly or in groups. When, as frequently happens, the original cyst does not produce scolices at all it is known as an *acephalocyst*. Sometimes the daughter cysts produce *grand-daughter cysts*, within which scolices are formed by gemmation from their walls. In other cases successive generations of *barren cysts* are formed as buds from the granular walls. Most commonly, the parent cyst contains *both* barren and scolex-bearing daughter or grand-daughter cysts. When the brood capsules develop *exogenously*, the resulting hydatid is a large lobulated cyst, each lobe either barren or containing numerous scolices. A special variety of the lobulated exogenous type is the so-called *multilocular hydatid*, which is met with in the liver and probably results from a fusion by compression of a number of exogenous brood capsules. It consists of a firm, solid, rounded mass, and if cut into exhibits numerous small irregular spaces separated by connective tissue and containing a transparent jelly-like substance.

The appearance presented by the *scolices* varies according to their

degree of contraction. When fully expanded they show a constriction about the middle, the anterior part consisting of suckers and hooks, and the posterior being comparable to the vesicle of an ordinary *Cysticercus*.

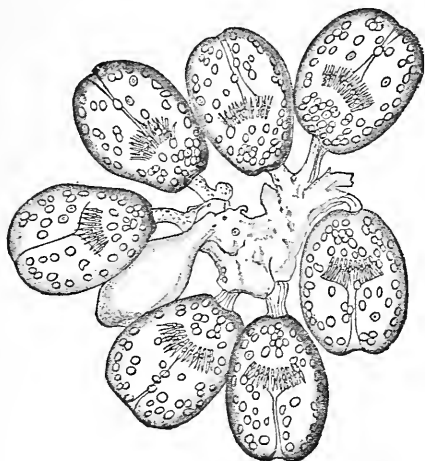


FIG. 12.—Scolices of *T. echinococcus*. (After Cobbold.)

The rostellum and hooks, however, are capable of retraction, a condition in which they are most frequently met with; they then have the form of oval granular bodies, about $\frac{1}{100}$ to $\frac{1}{60}$ inch in length, attached at one end by short stalks in groups to the cyst walls and having an aperture at the other end leading down to the retracted rostellum and hooks. The main difference between the *Cysticercus* of *T. solium* and that of *T. echinococcus*, therefore, lies in the fact that the latter forms many secondary and tertiary bladders each producing thousands of scolex heads, whilst the former is a

single, simple bladder giving rise to one scolex only. Each scolex head of the hydatid cyst is capable of developing into a *T. echinococcus* when introduced into the alimentary canal of the dog or wolf.

The hydatid cyst is most commonly met with in the liver, but occurs also, though less frequently, in the abdominal cavity, the pelvis, spleen, lungs, kidney, bladder, brain, and still more rarely in the bones of the body.

General characters of hydatid disease.

—The malady is of widespread distribution, being mainly conditioned in its occurrence by the uncleanly habits of the people in their relations with dogs, and the insufficient cleansing of raw vegetables grown in situations where they are exposed to the contamination of infected excreta. Statistics show the much greater prevalence of the disease in Australia and Iceland over other countries, although few, if any, are entirely exempt.

It has been met with at both extremes of age, even so young

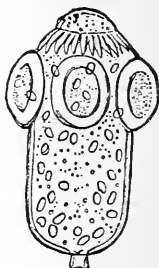


FIG. 13.—Separate scolex of *T. echinococcus*. (After Cobbold.)

as two years, but its greatest frequency is in adult life. Sex predisposes only so far as the habits of the individuals are concerned.

Symptoms.—The general clinical features of hydatid disease are those of a slowly growing tumour, giving rise to symptoms which are mainly those of pressure in proportion to its bulk and according to its situation. It is seldom, until they have attained considerable size, that they give rise to much discomfort, and, on the whole, they cause but little pain, and may even continue unrecognised during life. When sufficiently near the surface the physical signs of a cyst may be recognised, and it is sometimes possible to elicit what is known as the “hydatid fremitus or thrill”—a peculiar, palpable vibration, detected on percussion over the tumour. It may be perceived with cysts of other origin, and depends on the size of the growth, character of the contained fluid and nature of the surrounding tissues. The increasing bulk of the cyst tends to displace organs and to bulge the adjacent body walls compressing the structures, in proportion to the resistance offered by neighbouring parts.

The symptoms special to the different situations will be referred to under the several organs involved.

Terminations.—The ultimate course of the tumour is variable. In some positions, as the brain, it may soon prove fatal, but when involving less important organs and of a lengthy duration, the hydatid may die and undergo various forms of degeneration; the contents of the mother cyst ultimately becoming of a caseous or putty-like consistency, and later infiltrated with calcareous salts, a similar change having taken place in the cyst wall. A gelatiniform degeneration has been described as of occasional occurrence.

Less favourable than spontaneous death is rupture of the cyst and escape of the contents, causing peritonitis, pleurisy, or other complications, according to position; or it may be a communication is thereby established with one of the passages leading from the body, such as bronchus, bowel, or ureter.

Transudation of bile, urine, or other fluids of the body into a hydatid may take place, causing either the death of the parasite and the degenerative changes mentioned, or inducing suppuration and the conversion of the cyst into an abscess, a condition which is marked by rigors, pyrexia, and the general symptoms of pus formation. Unless opened, such an abscess is very liable to burst.

Diagnosis.—The recognition of a hydatid cyst, even when the cystic character of a swelling may be detected, is often largely based on probability and the exclusion of other causes of tumour. The absolute diagnosis must rest on the discovery of scolices, hooklets, or

shreds of the characteristic laminated cyst wall in the fluid withdrawn. The close similarity of the fluid to cerebro-spinal fluid renders its chemical examination of doubtful import when the cyst is connected with the brain or spinal cord, though of considerable value should it be located in the chest or abdomen.

The withdrawal of a small quantity of fluid from a hydatid cyst, however superficial, by a grooved needle or hypodermic syringe is a proceeding not wholly free from risk, inasmuch as severe and even fatal collapse have been not infrequently known to follow so seemingly simple an operation. This result has been attributed to the toxic effect of some ptomaine contained in the fluid, to which also is ascribed the appearance of an urticarial rash which often follows on puncture, as it may on the spontaneous rupture of the cyst.

Treatment.—The treatment of hydatid disease is essentially surgical. No drugs are of any service for the destruction of the parasite. Simple aspiration is sometimes sufficient, but it is often necessary to adopt the more radical treatment of incision or abdominal section and removal as far as possible. The situation of the cyst in some measure determines the plan selected, but although the death of the hydatid may be induced by simple puncture and withdrawal of the fluid, and in this way a cure may be effected, it has been found in practice that a large proportion of the cases so treated subsequently require incision or even more extensive treatment. The procedure, therefore, has fallen into disfavour amongst those who have had large experience of the disease. This plan, moreover, is actually dangerous of application in pulmonary hydatids owing to the liability of the fluid to escape into the bronchial tubes. The risk of collapse already referred to must not be forgotten. Free incision and drainage are imperative if suppuration have occurred.

NEMATODA

ASCARIS LUMBRICOIDES

The Round-worm is found in the small intestine, but may migrate into the colon or rectum or rarely into the stomach, œsophagus, trachea, bile duct, or gall bladder. The female *Ascaris* is about ten inches long, the male smaller. It is cylindrical in form, tapering at both ends, is marked longitudinally by four equidistant lines, one dorsal, one ventral, and two lateral, and is unsegmented. The mouth is terminal and is bounded by three small oral lobes; there are no hooks or suckers. The excretory pore is ventral and within the anterior fourth, the anus ventral

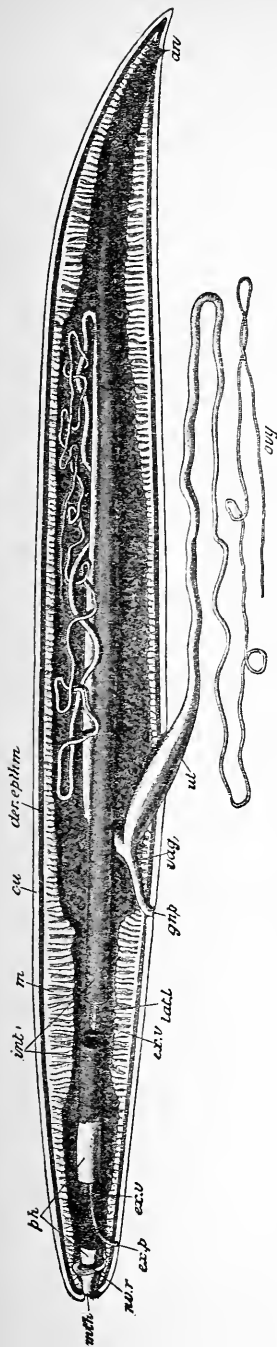


FIG. 14.—*Ascaris lumbricoides*. Semi-diagrammatic dissection of the female. *an*, anus; *cut.*, cuticle; *der. ephlm.*, der., epithelium; *ex. p.*, excretory pore; *ex. v.*, excretory vessel; *gonop.*, gonopore; *int.*, intestine, partly cut away; *lat. l.*, lateral line; *m.*, muscular layer; *mth.*, mouth; *ov.*, ovary; *ovr.*, ovary, that of the right side *in situ*, the left spread out; *ph.*, pharynx, partly cut away; *ut.*, uterus.

and posterior. In the male the genital duct opens into the rectum close to the anus, and there are two small penial setæ, whilst in the female it opens by a special pore at the junction of the anterior and middle thirds on the ventral side.

Structure.—There is a well-marked *body wall*, composed of a thick cuticle, a layer of epidermal cells, and four longitudinal muscles of a characteristic structure, occupying the intervals between the lines seen on the surface. Within the body wall is the *body cavity*, containing the alimentary canal, consisting of pharynx and intestine, and the coils of the well-developed genital system. In the *female* there is a pair of long, coiled, thread-like ovaries, each passing gradually into an oviduct and then into an uterus; the uteri join a short muscular vagina ending at the genital pore. In the *male* the arrangement is similar: a pair of coiled, thread-like testes, each passing into a vas deferens, which becomes continuous with a wide vesicula seminalis joining a single ejaculatory duct. The excretory system consists of two longitudinal canals occupying the lateral lines and joining anteriorly to open at the excretory pore. The nervous system is made up of a ring round the pharynx, giving off six nerves forwards and six backwards. Two of the latter are larger than the others and run along the whole length of the body occupying the dorsal and ventral lines.

Development.—A very large number of ova are discharged from a single *Ascaris*. They are oval in form and measure about $\frac{1}{340}$ inch in length and $\frac{1}{140}$ inch in width. They are fertilised in the uterus and pass

out with the *fæces* of the host. Development takes place directly without the intervention of a second host, and either the eggs containing the developing embryos or the latter themselves, after liberation, are taken into the human intestine by the drinking of water contaminated with *fæcal* matter.

Symptoms caused by *Ascarides*.—Although many symptoms have been supposed to be due to round-worms, they are as a rule ill-defined, and in not a few cases the first indication of the parasite is the discharge of a worm *per anum*. The main symptoms are those of intestinal irritation, which in children may be attended with febrile symptoms or reflex phenomena—such as convulsions, muscular twitchings, and grinding of the teeth, uneasy and disturbed sleep, picking at the nose, irritation at the anus; wasting and *anæmia* may in these cases be present. Rarely, more severe symptoms arise from the migration of the parasites. They may enter the stomach and be discharged by vomiting, or, by passing up the *œsophagus*, may enter the larynx and cause asphyxia, or if this is avoided they may enter a bronchus and produce gangrene of the lung. Occasionally they lead to complete obstruction of the bowel, or by perforating the intestine may lead to peritonitis. Sometimes they enter the bile duct and produce symptoms of biliary obstruction.

Treatment.—The best remedy against round-worms is *santonin*. Before employing it, fluid diet only should be allowed for a day and an aperient administered. *Santonin* may be given alone or mixed with sugar, or made into a syrup or in lozenges, in doses of 1 grain for a child and 2 to 5 grains for an adult, every morning for three or four days. This should be followed by a purgative. *Santonin* is said to be very efficacious when dissolved in castor-oil.

Precautions against infection, particularly in children, should be observed. Strict attention to cleanliness and the avoidance of impure water are necessary.

OXYURIS VERMICULARIS

This parasite is chiefly found in the rectum and colon, but also in the small intestine and the vermiform appendix. Thread-worms sometimes migrate from the anus into the vagina or urethra. The female is about one-third to one-half inch in length, the male about one-sixth inch. Anteriorly is the mouth, with three oral lobes and wing-like expansions of the integument, and in the male the tail is obtusely pointed and rolled up, whilst in the female it is long and narrow and three-pointed at its end. In the male the genitalia are situated posteriorly and the

duct opens into the rectum, but the female genital pore is far forward. Development is direct, the ova being taken in by the host as such and developing in the intestine. The ova, when deposited, already contain a developing embryo ; in shape they are asymmetrically oval, and are about $\frac{1}{500}$ inch long by $\frac{1}{1000}$ inch in diameter. Oxyurides occur chiefly in children and persons of dirty habits. Infection occurs through bad water, and from uncooked vegetables and salads, such as water-cress, by which the ova are conveyed ; and in children reinfection may occur through scratching the anus, and thus conveying the ova under the finger-nails to the mouth. From their frequent occurrence in the vermiform appendix, where they are often found at post-mortem examinations, even when there are none in other parts of the intestine, and from the fact that those found in this situation are mostly immature, it is probable that the appendix may serve as a breeding-place for thread-worms in children.

Symptoms caused by Oxyurides.—

The chief symptoms to which thread-worms give rise are an irritation or itching around the anus, coming on chiefly in the evening, with perhaps itching at the nose. There may be also restlessness or troubled sleep, with even convulsions or choreic symptoms ; loss of appetite, vomiting, abdominal pain, and anæmia may be present. The presence of oxyurides in the vermiform appendix may set up a certain amount of catarrhal inflammation of that part, with pain referred to the right iliac fossa and other symptoms simulating appendicitis.

Treatment.—Local treatment is generally all that is necessary. In children the injection of a strong solution of common salt or of quassia is generally quite sufficient. Other enemata may be employed, such as a strong infusion of green tea, carbolic acid, aloes, etc., and the remedy should be repeated from time to time. In some cases, however, such simple remedies fail, probably owing

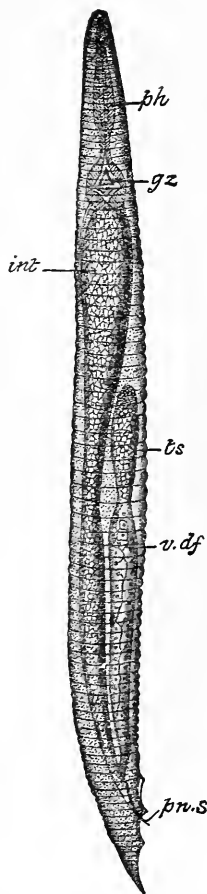


FIG. 15.—*Oxyuris*, from the right side. *gz.* gizzard ; *int.* intestine ; *ph.* pharynx ; *pn. s.* penial setæ ; *ts.* testis ; *v. df.* vas deferens. (From Shipley, after Galeb.)

to the parasite inhabiting the vermiform appendix and breeding there. In such cases treatment with repeated small doses of santonin, and purgatives, as in the case of *Ascaris*, may be tried. There are some cases which resist treatment for years, frequently recurring after the most careful precautions. The itching may often be allayed by smearing the anus with mercurial ointment, or with equal parts of Ung. Hydrarg. Oxid. rub. and Ung. Zinci, or with a weak solution of Liq. Carbonis detergens.

TRICHOCEPHALUS DISPAR

This is the Whip-worm, and occurs most frequently in the cæcum and upper part of the colon. It has a thread-like form, and is about one to one and a half inches long. The anterior end is long and hair-like, being much narrower than the posterior part, which in the male is spirally coiled, in the female straight and bluntly pointed. It is unsegmented, possesses an alimentary canal, body cavity, and genital organs, as in other Nematodes. Development is direct, the eggs discharged by the female passing out with the fæces of the host and developing in the intestine of another individual. The ova are oval in form with pointed ends, have a firm brownish-yellow shell, and are about $\frac{1}{500}$ inch long, by $\frac{1}{1000}$ inch in width.

Symptoms caused by Trichocephalus.—As a rule the Whip-worm does not give rise to any symptoms, and its presence is seldom diagnosed except by the discovery of the characteristic ova in the fæces. Sometimes, however, the parasite appears to be the cause of diarrhoea by producing intestinal catarrh, and severe anæmia has been attributed to it.

Treatment.—No treatment is, as a rule, needed; but if any should be required, the remedies used against *Ascaris lumbricoides* should be employed.

FILARIA SANGUINIS HOMINIS

The mature worm (sometimes called *Filaria Bancrofti*) is parasitic in warm climates in the human tissues, chiefly the lymphatics, and has been found in association with such diseases as chyluria, lymph-scrotum, and elephantiasis. It is about three to four inches long and of the thickness of a human hair. It has a narrow head and neck bearing a terminal mouth. In the female, which is larger than the male, the genital orifice is far forward. There is a straight alimentary canal lying in the body cavity and a ventral anus near the posterior extremity. The female genital organs include a muscular vagina, an uterus, two oviducts, and

looped ovarian tubes. The oviducts and uterus are usually found to be full of ova, with developing embryos. The male is both smaller and shorter than the female, and its tail shows a tendency to curl up. The intestine, which ends at an anus in the same position as in the female, receives the vas deferens just before it opens to the exterior, and two very slender spicules may sometimes be seen protruding from the common orifice. In both sexes the surface of the parasite is covered by a thin transparent cuticle of chitin (Plate I. Fig. 2).

Life-history.—Multitudes of larvæ are produced by the mature *Filaria* and pass into the blood, where they are known as the *Filaria sanguinis hominis*. These larvæ are about $\frac{1}{100}$ inch long and $\frac{1}{3500}$ inch in diameter, have a blunt anterior end and pointed tail, and are composed of an outer clear layer and central darker granular contents, without apparently any definite intestine or other organs. The clear outer layer forms a delicate structureless "sheath," considerably longer than the body of the embryo, and within which the latter is capable of movement to and fro. A portion of the sheath is, thus, generally unoccupied and collapsed, so as to trail after either the head or tail or both, according to the position of the embryo within it. The darker granular contents of the sheath form the body proper of the embryo, and on careful staining can be shown to consist of an outer delicately striated layer with a central mass of closely arranged cells, in which at three spots along its length can be distinguished darker irregular accumulations of granular matter, representing the rudiments of some of the internal viscera. They undergo no further development in the blood, and, unless transferred to an intermediate host, soon die. The next stage is the transference of the larvæ from man to the stomach of such blood-sucking insects as the mosquito. Here they undergo further development, partly in the insect's stomach, but also in its tissues, into which they migrate. The mosquito, after becoming gorged with blood, repairs to stagnant water, and the larval *Filariæ* ultimately escape into the water by the death of the mosquito. From the water they are received into the stomach of man, and, boring through its walls, are carried to the tissues, where the mature animal is found. Quite recently Dr. Low discovered a filarial worm in the proboscis of a mosquito; an observation that suggests that the worm enters the human body by the bite of the insect, in a manner similar to that which occurs in the case of the malarial parasite (*Brit. Med. Jl.* May 1900).

The worm was first found (1870) in the chylous urine of a patient suffering from elephantoid fever, and in 1872 the parasite itself was discovered in the blood by the late Surgeon-Major T. Lewis, and received the name of *Filaria sanguinis hominis*. At the present time at least six blood parasites of allied character are known.

They are: 1. The *Filaria sanguinis hominis nocturna*. This, the original parasite discovered by Lewis, is now named the *nocturna* owing

to its presence in the peripheral blood only at night. The worm appears in the blood soon after 5 P.M., and increases in numbers up to midnight, when several hundreds of the parasites may be found in each drop of blood, in active movement, though scarcely shifting their position. By eight or nine o'clock in the morning the filariæ have almost or quite disappeared from the cutaneous circulation, and may then be found, as Dr. Manson has shown, in the larger arteries and especially in the lungs, to a less degree in the capillaries of the heart, and yet more rarely in those of the brain, muscles, and kidneys; they appear to be completely absent from the liver, spleen, and bone marrow. No satisfactory explanation of this remarkable alternation in the distribution of the parasite in the circulation has hitherto been given, though several have been put forward, particularly one that attributes the phenomenon to the formation in the blood of some material "the outcome of the activities of working life"; for it has been observed that the invasion of the superficial blood stream becomes diurnal when the natural periods of sleep and working are reversed. It will be noted that this periodicity corresponds to the habits of the mosquito, which is an essential agent in the life-history of the parasite, and that a closely similar condition obtains in the *Plasmodium malariae*, another hæmatozoon dependent on the same agency for the completion of its life-cycle; it is remarkable, however, that the latter organism specially selects those organs during the day which the filaria avoids. There must, however, be something beyond an adaptation of parasite to mosquito, since another filaria (*F. diurna*) swarms in the peripheral circulation only during the day, and the *F. perstans* and others are constantly present both day and night.

This variety of filaria is of wide occurrence geographically, being met with in the inhabitants of all tropical and subtropical countries.

2. The *Filaria diurna*.—A worm similar in appearance to *F. nocturna*, but appearing in the peripheral blood during the day. It occurs in natives of the lower Niger region.

3. The *Filaria perstans*.—This parasite is present in the peripheral blood both by day and night. It is smaller than *F. nocturna*, measuring but $\frac{1}{125}$ inch in length and about $\frac{1}{5000}$ inch in breadth. The tail is blunt and no sheath has been observed. During its movements it not only betrays the wriggling movement common to all filariæ, but in addition it can be seen to find its way amongst the blood corpuscles and travel across the field of a microscopic specimen.

It occurs in the natives of the Congo district and Old Calabar. It is constantly found in the blood of persons suffering from sleeping sickness.

4. The *Filaria Demarquati* has been found in the blood of natives of St. Vincent, West Indies, and perhaps in natives of St. Lucia and New Guinea. It is present in the peripheral blood by day and night. In size it is much smaller than the *F. nocturna*.

5. The *Filaria Ozzardi*.—A parasite met with in the blood of Carib Indians inhabiting the hinterland of British Guiana. The embryo worm is present in the peripheral blood by day and night, and as elephantiasis is met with amongst the Carib Indians, it is probable that there is an association of cause and effect between the worm and the disease.

6. The *Filaria Magalhaesi* is the name given to a mature worm found by Professor Magalhaes in the ventricle of the heart of a child in Rio de Janeiro. The zoological characters of this parasite are as yet but ill understood. The embryo form has not hitherto been recognised, and it has been suggested that this may be the parental form of one or other of the two preceding varieties, which so far are unknown. It is to be noted also that the mature individual of *F. diurna* and of *F. perstans* have not been definitely ascertained, and consequently the life history of these parasites has yet to be determined.

FILARIASIS AND FILARIAL DISEASE

By filariasis is meant an infection of the human body by a species of filaria, and our knowledge of the condition is mostly connected with Dr. Manson's work on the *Filaria nocturna*. The immediate association between elephantiasis and the infection of the blood by the *F. nocturna* embryos is well-nigh established as one of cause and effect. But the *Filaria nocturna* itself is only the immature young of the parent worm the *Filaria Bancrofti*, and its presence in the blood is not always, in fact one might say it is exceptional for it to be, associated with evidence of disease; that is to say, *Filaria nocturna* may be present in the blood and give rise to no clinical evidence of the fact. How comes it, then, that the worm may lead to abscesses, varicose lymphatics, elephantiasis, and chylous urine? Dr. Manson has shown that it is not the worm, but the accidental expulsion of the immature ova that sets up a train of symptoms. The filaria is a viviparous animal, the young escaping from its body as mobile worms incapable of obstructing the lymph channels. If, however, the parent worm aborts and delivers the ova in the lymph stream whilst they are still ova, their size is such that they cannot be carried along freely, but may get caught in the vessels and create lymph stasis by obstruction. The abortion may be traumatic (the result of accident), and therefore it

is plain that it is not the presence of the parasite that causes the sequelæ of filariasis, but some fortuitous cause bringing about the premature expulsion of the ova.

Abscess.—When a parent worm (*F. Bancrofti*) dies a local abscess may be set up, and in a similar manner the blocking of the lymphatics by a group of immature ova may be so complete as to cause a local inflammation resulting in abscess. Such abscesses may occur subcutaneously or in any of the deep-seated tissues or organs of the body.

Varicose lymphatic glands.—In countries where filariæ prevail swelling, more especially of the inguinal glands, is not infrequently observed. One or both groins may be affected by single or multiple enlargements, which are soft and painless; but it may not be until adenitis develops that serious attention is directed to them. These gland lesions occur only in persons affected by filariæ in their blood, and the explanation of their being due to a plexiform fulness and hypertrophy of the lymphatics is no doubt correct.

Lymph scrotum.—The lymphatics of the surface of the scrotum and penis may become dilated and enlarged from filarial obstruction. In consequence the skin appears soft, smooth, and doughy, and the penile and scrotal tissues gradually hypertrophy. In course of time, in consequence of the oozing of lymph from the surface and subsequent scabbing and the formation of fissures and ulcers, the tissues become hard, indurated, and truly elephantine.

Hydrocele.—Associated with lymph scrotum a milky fluid usually collects in the tunica vaginalis; and the quantity may be so great as to constitute a hydrocele. On the other hand, a true lymphoid hydrocele containing a chyliferous fluid may occur independently of any other local sign of filarial disease.

Chyluria.—During the course of a case of filarial disease, the urine may suddenly assume a creamy appearance and consistence, white clots appear in the urine, and a stoppage of micturition may result owing to the coagulated masses blocking the urethra. Accompanying the chyluria there may be feverishness, backache, and pains over the renal region in addition to the mechanical difficulties. Chylous urine soon after being passed speedily separates into a fluid and a solid part. The solid portion consists of a stringy fibrinous coagulum of a white or pinkish colour. When examined microscopically the deposit is seen to consist of bladder epithelium, a few red and white blood corpuscles, and a fatty material of an undetermined nature. Urinary salts fall to the bottom of the vessel, and

the creamy-coloured fluid on the top yields an albuminous precipitate on boiling. Filariæ are to be found in both the solid and fluid material of the urine, which retain their mobility for many hours after evacuation. The train of symptoms appertaining to chyluria indicates an infection and obstruction of the lymph channels of the urinary tract, and implies a wide-spread implication of the lymphatics and glands in the retroperitoneal regions.

Chyluria may occur without any previous indication that the person voiding chylous urine was the subject of filariasis. The affection appears and disappears in an irregular manner; after continuing for days, weeks, or months, it may disappear only to return at intervals equally erratic. The exciting cause of chyluria, in persons suffering from filariasis, has been described, without sufficient reason, to local pressure due to such cases as parturition, violent exercise, or injury.

Elephantoid fever.—Accompanying all filarial affections, what has been termed “elephantoid fever” by Fayrer sooner or later occurs. As a sequela to each attack the area or areas in which the disease finds expression shows an accession of disturbance; the lymph scrotum is increased in bulk, the lymphatic glands attain a larger size, or the subcutaneous tissues of an extremity are further thickened. During the attack of fever lymphangitis and adenitis are made manifest by pain and swelling, redness, and increased temperature. Chyluria may also appear, betokening an implication of the pelvic or abdominal lymphatics. There are the usual signs and symptoms of fever—vomiting, restlessness, delirium, rigors, quickened pulse, and increased temperature, which after a few hours or a few days pass off with profuse sweating.

Elephantiasis of the extremities.—Although any part of the subdermal tissues may become elephantine, the lower extremities are much more frequently attacked than the upper. The dorsum of the foot early betrays signs of subdermal thickening, the part becoming hard, dense, or incompressible. During each succeeding attack of elephantoid fever the lymphatic tracts in the limb are red, swollen, and painful; the glands towards which they converge become enlarged and tender, and as the feverish outburst subsides, it is found that the area of hypertrophy has extended. Vesicles form on the hardened skin, containing a milky fluid, which, when the vesicles burst, dries into a crust or scab; abscesses not infrequently occur; a varicose condition of the lymphatics may ensue, giving rise to the “varix lymphaticus” and “nævoid elephantiasis” of some writers. In time the limb may become enormous; the muscles

waste ; from fissures and cracks a serous and lymphoid oozing takes place, mixed occasionally with blood, which cakes and crusts, showing ulcerating surfaces beneath.

Elephantiasis scroti.—The lax tissue, dependent position, and the rich lymphatic endowment of the scrotum render the parts specially liable to become elephantine. A lymph scrotum or frequent attacks of lymphangitis may serve as the starting-point, but with each successive attack of fever the bulk is added to, until the skin and subcutaneous tissues become thickened and hardened and the surface corrugated, fissured, and ulcerated. Combined with this condition the inguinal lymphatic glands become hypertrophied, or a hydrocele with chylous contents, or a hernia may occur and complicate the treatment. From the first, but more usually subsequently, the coverings of the penis are involved, until in time the penis becomes deeply imbedded in the mass, and the urine finds its way to the surface through a channel of hypertrophied prepuce many inches long. The scrotum may occasionally attain a weight of over 100 lbs., and the writer has removed a scrotal tumour which weighed 49 lbs. when emptied of blood and serous fluid.

Treatment of filariasis and its sequelæ.—No drug is known to exercise any curative power when the blood is infected by filaria. The various manifestations of the disease are to be treated on general principles.

ABSCESSES are to be opened, when their presence is manifested, whether they appear beneath the skin, in the deeper parts of the body, or in the abdominal viscera. It occasionally happens that a parent worm (*Filaria Bancrofti*) is found in the abscess. *Hydrocele* is to be tapped in the conventional method, but attempts at radical cure by injection with iodine or by excision are not expedient. It must be remembered that the escape of a milky fluid during the operation for what looks a simple hydrocele may be the first intimation that the patient is the subject of filaria. *Elephantoid fever* must be dealt with by the usual antifebrile regimen. The pain accompanying the fever, more especially in the back and groins, demands the application of hot fomentations, and, if severe, hypodermic injections of morphia. The temperature may rise to 103° or 105° , when antipyrin or phenacetin will be found to have a speedy and beneficial effect in controlling the fever. Vomiting and retching may be distressing, which sucking of ice and counter-irritation over the stomach will serve to relieve. Lymphangitis and adenitis are benefited by local applications of heat, belladonna liniment, etc. The treatment of *chyluria* resolves itself into rest, warmth, fluid

nourishment, plentiful warm drinks, and elevation of the pelvis. Drugs have not been shown to affect the condition in any way, although benzoic acid, thymol, methylene blue, and many others have found advocates. In the case of complete retention the passage of a catheter and washing out of the bladder may be demanded, or even perineal cystotomy. *Elephantiasis* of the extremities may be alleviated by elevation of the limb and firm bandaging; leeching, blistering, blood-letting, ligature of the main artery have been practised with doubtful benefit. To relieve the patient of a weighty and cumbrous limb amputation may have to be resorted to.

Elephantiasis of the scrotum lends itself to surgical treatment. The part may be removed with but moderate hæmorrhage and but little danger to life. The removal has to be undertaken with due appreciation of the fact that a hernia may be present in the tumour, that large hydroceles may exist, and that the testicles may be diseased. The operation is usually attended by satisfactory results, the testicles and penis being covered subsequently by cicatrical tissues, which seldom take on lymphatic thickening, and allowing, if the testicles have not been diseased or removed, of procreation.

NEGRO OR AFRICAN LETHARGY

SYN. SLEEPING SICKNESS

An almost certainly fatal disease confined to natives of the basin of the Congo and adjacent districts, characterised by a gradually-increasing lethargy, mental stupor, enlargement of the cervical glands, a skin eruption, and marked pruritus. In the blood of persons suffering from sleeping sickness a filarial parasite, the *Filaria perstans*, is found.

Geographical distribution.—The region of the West Coast and hinterland of Africa, in which sleeping sickness prevails, is the wide stretch of country which lies between the Senegal and Loanda rivers to the north and south respectively, and inland as far as the Stanley Falls on the Congo, some 1000 miles from the sea. In this area, and possibly beyond it, the sleeping sickness occurs in endemic

areas, attacking some villages with great severity, whilst in others the population seem to be immune from the fact that the disease has not been known to occur with any virulence amongst them.

Cases of sleeping sickness have been met with beyond the African shore, in the West Indies, in the United States of America, Brazil, and even in Britain. (Dr. Manson mentions having seen the disease develop in a negro boy at a school in Wales.) But it has invariably occurred that the individuals affected had for some period resided in the African area above mentioned. These outbreaks, therefore, go to show a lengthy period of incubation and not a wide geographical area of endemicity.

Etiology.—The *Filaria perstans* is a common blood parasite in the district in which sleeping sickness is endemic; so common in fact that as many as 50 per cent of the inhabitants of the district have the worm in their blood. Although in the blood of every person, hitherto examined, who suffers from the sleeping sickness the *Filaria perstans* has been found, and the two might appear to stand in the relation of cause and effect, yet is it the case that many persons with this parasite in their blood exhibit no symptoms of any disease. In other words, although all persons suffering from the sleeping sickness have the *Filaria perstans* in their blood, the converse is not true. We must therefore reserve judgment, and accept the possibility that some as yet unknown factor is requisite to explain how *Filaria perstans* causes, if it does actually cause, sleeping sickness to develop.

Symptoms.—The onset of sleeping sickness is marked by a change in the appearance, habit, gait, manner, and mental state of the person affected. In appearance the patient assumes a melancholy cast of countenance, the features generally are obscured and puffy, and the upper eyelid appears to droop, as in a person but half roused from sleep. The patient's habits change; he lies longer abed, wants to rest on all occasions, shows a desire to go to sleep, and is disinclined to do his daily work. The gait of the patient becomes shuffling, the knees seem to give way, and he behaves like a person drugged by opium or overcome by alcohol. The patient's manner also changes; as the disease advances he seeks to avoid company, does not want to talk, becomes morose, and only wants to be left alone to sleep. The mental state of the patient varies. Usually the development of the disease is gradual, but occasionally, and, as Dr. Manson remarks, by no means rarely, the disease is ushered in by what resembles acute mania, or by convulsions which appear epileptiform in character.

What may be termed concomitant conditions are : enlargement of the cervical lymphatic glands, especially of those behind the sterno-mastoid, so much so that the rather stiff movements of the neck are attributed to the irritation set up by them ; intense pruritus of the body generally, the skin at the same time appearing dry, and showing in many places a minute crop of papules. Patches of cutaneous anæsthesia are occasionally met with.

Muscular tremors may develop early, but always appear later in the disease. Meanwhile the ordinary reflexes remain intact. Nutrition is not impaired, and it is not until later that the general health suffers.

Two negro patients (*Brit. Med. J.* Dec. 16, 1899), under observation in Charing Cross Hospital, afforded excellent opportunities of studying the progress of this peculiar disease. The general state of stupor was well marked ; the patient, whilst spoken to, would drop off in apparent sleep ; when eating, the morsel in the mouth might be neglected, and the patient would cease to chew for an indefinite time, staring meanwhile straight before him. When spoken to, or roused in any way, as by nudging him, the patient would again proceed to masticate as if no interruption had taken place. Even whilst raising food to the mouth in a spoon, or by the hand, the arm became arrested at times, and maintained in a fixed position for a period, in fact, until something occurred to recall the patient to his surroundings.

Slowness of speech, apparently due to a sense of fatigue and drowsiness, and attended by a prolonged reaction period, as judged by the time between question and answer, are noticeable features. Pain may or may not harass the sufferer during the last few weeks of life. When it does occur it is apt to be severe, alternating with unconscious periods during the convulsive seizures.

The body temperature is either normal, subnormal, or but very slightly raised, until just towards the end of life, when there is usually pyrexia, and even hyperpyrexia. The pulse denotes low arterial pressure. Occasionally the patient becomes more lively, and it would appear as though the disease was subsiding in yielding to treatment. The improvement, however, is illusory. In time the patient is confined altogether to bed ; he loses flesh, convulsions or tetanic contractions of certain muscles obtain. Diarrhoea, and perhaps bed sores supervene, and the patient may die of exhaustion, or during a convulsive seizure.

Pathology.—In the blood of persons suffering from sleeping sickness, so far as investigations have gone, malarial parasites have

not been seen. In the fæces the ova of *Ascaris lumbricoides*, *Trichocephalus dispar*, *Ankylostoma duodenale*, and other intestinal parasites are found in most of these patients, as in almost all negroes from the West Coast of Africa.

The estimation of the red blood corpuscles gave, in one case of Dr. Manson's, 5,300,000, and in another 4,500,000 per c.mm., the value of the hæmoglobin in the same cases being 60 and 50 per cent respectively.

Our knowledge of the pathological changes is chiefly based on the post-mortem examination of the two foregoing cases. The general conclusions are, that the symptoms are due to a diffuse meningo-encephalo-myelitis (probably of infective origin), and chronic in its nature. The peri-vascular lymphatics of the central nervous system are stated to be crowded with mononuclear lymphocytes, but, with the exception of a proliferation of lymphocytes in the lymphatic glands generally, and an increase in the size of the lymphoid nodules in the duodenum, no other visceral changes have been observed. Parent filarial worms have been met with in an abscess cavity in the lung, in the retro-peritoneal tissue near the aorta, and at the root of the mesentery. Living embryo filariæ were found in the cerebro-spinal fluid thirty-six hours after removal from the body; but as the fluid contained some blood, it is possible the filariæ gained entrance with it. The knowledge gained by morbid anatomy and bacteriological investigations do not serve to elucidate the cause of the disease. Bacteriology gave negative results in the cases at Charing Cross Hospital; but French investigators claim to have isolated a bacillus from the blood, although this result was unconfirmed by subsequent observers. The lethargy characteristic of the disease may be explained either by the fact of a toxic agent in the cerebro-spinal fluid acting upon the nerve centres, or by the interference with the metabolism of the nerve cells, owing to the accumulation of lymphocytes around the blood-vessels supplying the nerve elements. Nucleated bodies were found in the motor area of the cortex, especially in the peri-cellular spaces, when the brain tissue was treated by the Nissl method. The columns of Meynert were in one case found preserved, in another disorganised. The medulla appeared congested, showed profound evidence of chronic inflammation around the blood-vessels, and the nerve cells were atrophied or exhibited chromatolysis so much so that not many normal cells were to be found. The spinal cord in one case showed slight diffuse sclerosis in the pyramidal tracts with recent degenerated fibres; in both the spinal ganglia gave evidence

of chronic inflammation, and the central canal of the spinal cord was full of proliferated glia tissue.

The evidence that the *Filaria perstans* stands to sleeping sickness in the relation of cause and effect is not borne out by pathological investigation, and it is possible that an "infectious organism exists for which a suitable stain has not yet been found" (Dr. Mott). The reputed increase in size, said to have been noted in the pineal and pituitary bodies, is not confirmed by recent observations.

Diagnosis.—Beri-beri is the only known disease likely to be confounded with negro lethargy. The clinical features of the two diseases are, however, quite at variance. A resemblance to pellagra has been also referred to by some writers.

Prognosis.—So far as is known, all persons attacked by sleeping sickness die.

Treatment.—Temporary relief and benefit seems to result from the administration of santonin or thymol, by which means the intestines are relieved of their parasites or their ova. Excision of cervical glands, hypodermic injection of testicular fluid, administration of arsenic, and of a preparation of pituitary body, have all failed to cure.

DRACUNCULUS MEDINENSIS

When mature the guinea-worm inhabits the subcutaneous connective tissues of man in warm climates, such as the coast of Guinea, Abyssinia, Upper Egypt, certain regions of India, Persia, etc. It is from one to six feet long, and $\frac{1}{16}$ inch in thickness and of cylindrical form. The head bears a mouth bordered by four oral papillæ, and the posterior end is curved and pointed. It produces an enormous number of ova, which develop viviparously, and are discharged from the human host in the pus from the subcutaneous abscesses which the parasites produce. After discharging ova the worm will often leave the host through the small ulcer resulting from the bursting of the abscess. The females only are known, and it has been suggested that these are really hermaphrodites in which the male organs mature before the female. After their discharge the embryos reach some stagnant water and bore through the soft skin between the segments of a small Crustacean (*Cyclops*), and reach the body cavity of their new host. Here they grow, but do not attain sexual maturity. With their Crustacean host they next enter the alimentary canal of man and mature. It is said that after copulation the males perish, whilst the females migrate from the alimentary canal into the subcutaneous tissue, chiefly of the legs and feet, which are the parts of the body of barefooted natives most frequently brought into contact with water, which is essential for

the developing worms. This is probably the correct explanation of the presence of females only in the tissues of man.

Symptoms of Dracontiasis.—Until the worm reaches the surface and causes ulceration, few if any symptoms may occur. A local feeling, as of something beneath the skin, may be noticed, or even a slight eruption. Should, however, the parasite be injured, and its contained embryos escape into the tissues, serious results may follow, such as abscess, sloughing, and severe general disturbance. Sometimes the worm spontaneously dies *in situ* without discharging its ova; it may then become calcified, or slowly absorbed, and cause no symptoms.

Treatment.—No attempt should be made to extract the worm until complete parturition has taken place, which usually lasts over two or three weeks, lest it be broken and the embryos escape with the results described. The discharge of ova is to be encouraged by frequent douching with cold water and water dressings. When the parasite begins to emerge, slight traction and winding on a stick are permissible. Recently success has attended the subcutaneous injection of the worm, so soon as its presence is recognised, with a 1 in 1000 solution of mercuric perchloride, by which it is killed and subsequently absorbed without causing suppuration.

DOCHMIUS OR ANKYLOSTOMA DUODENALE

This is a small Nematode which inhabits the duodenum and other

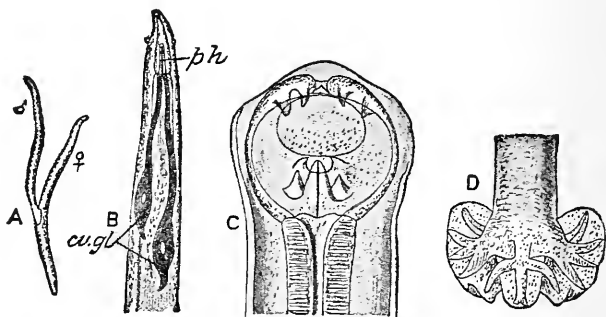


FIG. 16.—*Dochmius duodenalis*. A, male and female in coitu; B, anterior end, showing, *cv. gl.* cervical glands; *ph.* pharynx; C, mouth with spines; D, posterior end of male, with bursa. (After Leuckart.)

parts of the small intestine of man in most warm climates, especially Egypt, Ceylon, and India. Severe outbreaks occurred among the work-

men employed in the construction of the St. Gothard tunnel, as well as miners in Belgium and France, and brickmakers in Austria and Germany. The worm attaches itself to the intestinal wall, and by sucking blood from the host produces a severe, and often fatal, form of chlorosis. It measures about half an inch; the head is pointed and tapering, and the mouth is ventral. The oral orifice is armed with four asymmetrical teeth. The posterior end is blunt, and in the male bears a bilobed *bursa copulatrix* supported by eleven chitinous rays, and surrounding the anus and genital pore. In the female the genital aperture is far forward. The pharynx receives the ducts of a pair of *cervical glands*, whose function is unknown. The ova develop viviparously, and are discharged with the fæces of the host. In the fæces the ova may be readily recognised. They are oval in form, have a thin transparent egg membrane, and measure about $\frac{1}{600}$ inch in length by $\frac{1}{1000}$ inch in diameter. Within the egg shell the ovum body may be found in various stages of cleavage. After living for a time and growing in water or damp earth, the larvæ are transferred in impure water to the alimentary canal of man, where they develop sexual organs and mature; the same is said to occur outside the body in a suitable soil. There is no intermediate host.

ANKYLOSTOMIASIS

This term is applied to the train of symptoms and cachexia determined by the presence of the parasite in the small intestine. As with many other parasitic inhabitants of the alimentary canal, the extent to which the host may suffer is most variable; several species of worms, including the ankylostoma, may be found in the body after death, their presence having been entirely unsuspected during life, whilst on the contrary severe or fatal symptoms may result from their invasion.

Owing to the wounds of the intestinal mucosa inflicted by the ankylostoma, a progressive anæmia develops which tends to assume in its clinical features a pernicious type, though differing from true pernicious anæmia in the absence of wasting and the character of the blood, the hæmoglobin index falling and there being no special poikilocytosis. Irregular febrile attacks, peripheral œdema, dyspnœa, palpitation, lassitude and muscular weakness, and even retinal hæmorrhages, mark the progress of the case, added to which there

are dyspeptic symptoms, such as a capricious or excessive appetite, colic, irregularity of the bowels, and motions frequently containing altered blood, and ova of the worm. The duration is generally chronic, although cases may run a fatal course of a few weeks or months.

Treatment.—Thymol in 20 grain doses in cachet is the most efficacious drug to bring about the expulsion of this parasite. For a day or two previously to its administration the patient should be kept on a low diet, and a purgative should be given the night before. Three or four doses at intervals of an hour, and succeeded, if necessary, in four hours by another aperient is the plan usually followed, and this may require repetition in the course of a week, if ova appear in the fæces. The toxic effects of thymol when absorbed into the blood should be remembered, and these are best avoided by the patient keeping at rest and avoiding alcohol or other solvents whilst under treatment. As with other parasitic entozoa, prevention should be aimed at by the careful selection of drinking water, which should be boiled.

TRICHINA SPIRALIS

In its mature condition this parasite is found in the intestine of man, pig, rat, and other mammals, and there produces large numbers of embryos, which migrate into the muscles of the same host and become encysted. The mature worm is very small, and measures, the male about $\frac{1}{16}$ inch, the female about $\frac{1}{8}$ inch. The body is cylindrical and thread-like, with a mouth at the anterior pointed end, and an anus at the broader posterior extremity. The male has a bilobed caudal appendage near the anus, where the genital duct opens. The female is stouter and its genital pore is anterior; its genital system includes an ovary, oviduct, and large uterus, within which the embryos develop viviparously. As ordinarily seen, the embryo *Trichinæ* consist of minute spirally coiled worms lying within oval cysts, just visible to the naked eye as white specks in the muscles of the affected animal. The embryo is about $\frac{1}{35}$ inch long, is somewhat pointed anteriorly, and has a blunt posterior end. The cyst in which it lies is about $\frac{1}{10}$ inch long, and its walls are transparent, and laminated. The cyst walls become more or less calcified. They lie within the sarcolemma, which undergoes some thickening over them, and in advanced specimens the intestine and genitalia of the embryos are discernible.

Life-history.—Man becomes infected by eating trichinosed pork, and the encysted embryos are liberated from their capsules and mature after a few days in the intestine. The females produce ova, and after fertilisation these develop in the uterus into minute

embryos, which on their discharge attach themselves to the mucous membrane, penetrate the intestine, and are carried in the blood-vessels or lymphatics to the muscle fibres where they become encysted. The cyst is in no way a part of the parasite itself, but is formed by an inflammatory change set up by the irritation of the embryos and resembles the spurious fibrous capsule which surrounds the true hydatid cyst. Examination of affected muscles shows a considerable destruction of the fibres, and an increase of the interstitial connective tissue. Sometimes a single cyst contains two or more embryos. The progress of their life-history is rapid. The embryos, which begin to be discharged within a few days of infection, have reached their destination in the muscles by about the end of the second week, and at the end of a month or five weeks have become encysted. No further change occurs until the trichinosed muscles reach the alimentary canal of a new host. The pig becomes trichinosed from the flesh of the rat.

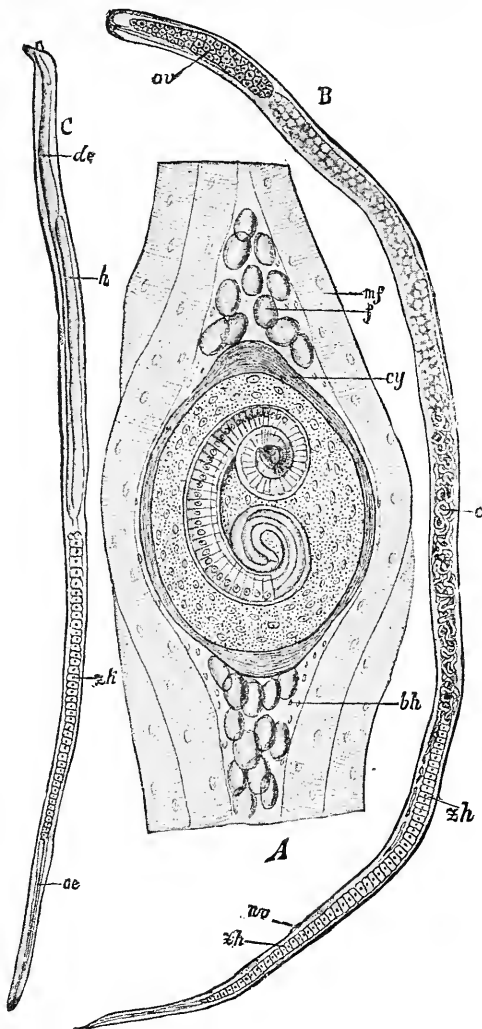


FIG. 17.—*Trichina spiralis*. A, encysted form, in muscle of host; B, female; C, male. *bh.* connective tissue envelope; *cy.* cyst; *de.* ejaculatory duct; *e.* embryos; *f.* fat globules; *h.* testis; *mf.* muscle fibre; *oe.* pharynx; *ov.* ovary; *wo.* gonopore; *zh.* cell masses in intestine. (From Lang's *Comparative Anatomy*, after Claus.)

TRICHINIASIS

Trichiniasis, the disease resulting from the eating of trichinosed flesh, is not common in this country, but in Germany and elsewhere, where the flesh of swine is consumed in an uncooked or undercooked condition, it is frequently met with.

Symptoms.—Within a day or two after eating the infected flesh, the patient generally suffers from gastro-intestinal symptoms, complaining of severe pressure in the stomach, of eructations and nausea, with a feeling of heaviness and depression. There is usually diarrhoea with severe colicky pain, sometimes so aggravated as to resemble cholera. These symptoms, which are accompanied by some febrile disturbance, last about a week or ten days, and are due to the hatching of a young brood of *Trichinæ* and their commencing migration. Shortly the symptoms of gastro-intestinal disturbance are accompanied or succeeded by vague muscular pains. The affected muscles swell, become stiff, hard, rigid, and tender. With these pains there is a peculiar œdema of the subcutaneous connective tissue beginning in the face and chiefly the eyelids, and spreading thence to the extremities and even the serous cavities. Sometimes the patient assumes a characteristic attitude, lying on the back with shoulders and elbows sharply flexed and hands slightly flexed, but with hip joints and knees nearly straight, so that he becomes unable to lift his arms, extend his forearms, bend the knees or sit up without severe pain. Sometimes, in the third or fourth week of the disease, there are symptoms showing that the muscles of respiration, of the glottis, of the pharynx or tongue, or of mastication are affected. The temperature is generally markedly raised during the continuance of the muscular symptoms, but is sometimes almost unaffected. When there is much fever the general course of the chart somewhat resembles that of enteric fever with morning remissions. After about the fourth or fifth week the symptoms usually abate; the muscles become less rigid and painful; the temperature falls; appetite returns, and the patient recovers. In some cases there is an insidious onset, with no intestinal symptoms, and at first only vague muscular pains and stiffness. In some epidemics of trichiniasis the mortality has been very slight, but in others there has been a death-rate as high as 25 per cent. The chief causes of a fatal issue are enteritis, peritonitis, intercurrent pneumonia, debility and exhaustion.

Diagnosis.—The diseases with which trichiniasis is most likely to be confounded are—enteric fever, acute rheumatism, or acute tuberculosis. It has also been mistaken for cholera. A careful attention to the course and symptoms, particularly the severe muscular pains and the œdema of the face, and absence of joint affections will, however, suffice to establish the diagnosis. By a careful examination of the stools the *Trichinæ* may be detected as small white threads, and it is permissible, when in doubt, to harpoon one of the muscles and submit it to microscopical examination.

Dr. Thomas Brown, of Baltimore, suggests that an examination of the blood in cases of doubtful trichiniasis may afford a positive diagnostic sign, for he found from an examination of three cases that there is a great increase of the white cells, and further that there is a remarkable relative and absolute increase of the eosinophile corpuscles. Whereas the normal proportion of eosinophiles to all white cells is about 2 to 4 per cent, he found that in trichiniasis the proportion of eosinophiles rose to 35 per cent, and even to 68 per cent in one case where the symptoms were at their height, and that the percentage gradually fell as the symptoms abated.

Treatment.—Unfortunately we do not possess a drug which has the power of destroying *Trichinæ* without injury to the patient. If their presence be suspected sufficiently early it may be worth attempting to dislodge the intestinal parasites by the use of remedies useful in treating other intestinal worms, but when the embryos have reached the muscles it is impossible to destroy them. The treatment of an attack of trichiniasis must therefore be conducted on general principles, as for other affections consisting of a local inflammation with fever. The prophylactic treatment is obvious, the avoidance of pork having any suspicion of trichinosis, and particularly of pork which has been improperly cooked. Smoked ham and German sausages, unless well cooked, are common sources of infection. *Trichina* cysts in pork are visible to the naked eye, as small white, round, or oval specks, and generally in pigs affect the diaphragm first, so that an examination of a suspected carcase should begin with that muscle, portions of which should be microscopically examined.

T. W. SHORE.
JAMES CANTLIE.

*DISEASES DETERMINED BY POISONS INTRODUCED
INTO THE BODY AS SUCH*

By a poison is understood whatever gains access to the body and interferes with the proper and satisfactory working of its various functions, exclusive of those substances which produce injurious effects solely of a mechanical character. Such materials may obtain entrance from the outside—poisons of extrinsic origin—mainly with the food and air, and are absorbed into the blood from the gastro-intestinal or respiratory tracts. Or they may be developed in the tissues or intestines, as the results of morbid metabolism or perverted digestive processes—poisons of intrinsic origin or autogenetic poisons. Intermediate, as it were, between these two groups are the toxins of microbic origin, which are formed in the body by specific micro-organisms that have invaded the tissues from without.

In considering the effects produced by the various toxic substances included within these groups, regard must be had both to the material itself and to the individual poisoned. Of the former a sufficient dose is requisite, the amount varying in every case, whilst the latter may exhibit wide variations in the degree of susceptibility, or of resistance to the action of the poison. By certain procedures the natural resistance may be so increased that complete immunity may be obtained, and although this is not applicable to all noxious substances, it specially obtains in respect to many of the microbic toxins, and may be observed with such bodies as alcohol, opium, cocaine, arsenic, and antimony, to which the individual, by habitual drugging, may become inured.

The widest range of symptoms follows on the introduction or development of the different toxic agents. Whilst some act with exceeding rapidity, others require days or hours; some, such as the corrosive poisons, produce serious local damage, to which general symptoms may later succeed; others lead to their characteristic effects on the various systems—nervous, cardio-respiratory, excretory, etc., without any obvious local lesion. Sooner or later they are eliminated, either unaltered or having undergone considerable changes in composition, and the ill results which follow their circulation in the body are not infrequently to be attributed to impaired conditions of the excretory organs, whereby their removal is interfered with. Nor are their results always confined to their own direct influence;

it may be that the conditions of ill health, which their presence determines, favour the action of other noxious materials which thus may be regarded as secondary and cumulative, the final effects being attributable to both causes. The grave course of acute pneumonia in a subject of chronic alcoholism, or the liability to whooping-cough which an attack of measles confers, illustrate this.

No very satisfactory classification of poisons of extrinsic origin (exclusive of microbic) can be made, and on grounds of convenience only the following arrangement is adopted :—

1. Food poisons ; 2. Alcohol ; 3. Drugs (which may be further subdivided according to their mineral, vegetable, or animal origin ; or to the general character of the symptoms to which they give rise, *e.g.* corrosive, irritant, narcotic, etc.) ; 4. Gases ; 5. Snake venom.

The acute conditions determined by large doses of most of these poisons form the subject-matter of works devoted to toxicology. Here space only permits the consideration of those more chronic states of disease brought about by repeatedly taken small quantities, producing a cumulative effect, sometimes of an obviously structural character.

FOOD POISONING

As a vehicle for the entrance into the body of toxic agents, the food stands foremost. Such diseases as summer diarrhoea, typhoid fever, and cholera, almost entirely, and to a lesser degree tubercle, are produced by means of infected food. In most cases of lead poisoning, also, the injurious substance is taken with the food, and by the same means most parasitic entozoa are introduced. But by "food poisoning" is conventionally understood those toxic effects due, not so much to accidental contamination of the ingesta, but to changes of a poisonous character in certain articles of diet themselves, though this definition does not pretend to strictness.

MEAT POISONING.—Outbreaks of illness, often serious and frequently fatal, following on the ingestion of certain meat foods, have long been known. Such articles as meat pies, especially of pork or veal, tinned meat and fish, sausages, particularly in Germany, and mussels are those which have commonly been held responsible for the epidemics ; and it was further noticed that they had been imperfectly cooked, and very frequently produced their ill effects when partaken of cold ; but it by no means follows that these substances give obvious evidence of being tainted. The late Dr. Ballard, who first gave an explanation of these outbreaks, attributed the poisonous

results to contamination of the food in the dirty larders and places in which they were stored, and it is possible that this may sometimes be the case. More precisely, they appear to be due to one of two causes—(a) the putrefactive decomposition of proteids, which give rise, among other substances, to such bodies as neurine, choline, muscarine, etc., classed as animal alkaloids or ptomaines, and also certain albumoses. It is to similar compounds that the toxic properties of mushrooms are due. (β) The infection of the meat by specific organisms, as *bacillus enteritidis* (of Gärtner), and the *B. botulinus* (of Van Ermengem), such meats giving no evidence of putrefaction or unsoundness. Much information, in respect to this source of toxicity, is due to the work of Mr. Herbert Durham (*Clinical Journal*, June 7, 1899).

Symptoms.—The effects of these poisons, which set in suddenly and quickly when alkaloidal, are mainly manifested on the alimentary canal, causing a gastro-enteritis of severe or even fatal character. Vomiting, purging, sometimes with bloody stools, abdominal cramps, sweatings, quick soft pulse, prostration and profound collapse, are met with in a greater or lesser degree; and since these symptoms are sometimes accompanied by pyrexia, conditions are established which resemble cholera or even typhoid fever, with which specific infections these meat microbic poisonings are closely allied.

Some of the alkaloids cause severe nervous symptoms in addition or with preponderant intensity, and convulsions, tetanic spasms, paralyses, coma, etc., have been observed; others appear chiefly to affect the heart or the cardio-respiratory mechanism.

Since, in the majority of cases, these effects are avoided by thorough cooking, the indication for prevention is obvious. When once established, the **treatment** of the affections must be symptomatic; the diarrhoea may require to be assisted by a dose of castor-oil for the more rapid elimination of the poison, combined with opium (*e.g.* tinct. chloroformi and morphinæ) for the relief of the pain, whilst the liability to collapse must be met with stimulants, alcoholic by the mouth, or ether or brandy subcutaneously.

POISONING DUE TO BAD CEREALS is of rare occurrence in this country at the present day, and is chiefly to be met with in regions in which the natives are existing in the most unfavourable hygienic conditions. The chief effects of these toxic substances are referable to lesions of the spinal cord, which have been more or less definitely recognised, and correspond somewhat closely to those which are attributed to the toxins of the specific infective diseases.

ERGOTISM, a disease now almost unknown, except in parts of Russia, was formerly a frequently recurring scourge in most countries of Europe, especially in those where rye bread formed the staple food, and was responsible for the deaths of hundreds of thousands and of indescribable misery and suffering. Its causation, first recognised more than two centuries ago, is a parasite of the rye—*Claviceps purpurea*—which is ground up along with the grains and so contaminates the flour. The ergot spurs appear to contain at least two toxic materials, cornutine and sphacelinic acid, to the preponderance of one or other of which the difference in the resulting symptoms has been attributed. The poison affects equally both sexes and all ages, and produces its effects, in part at least, by the extreme contraction of the arterioles, as well as of other plain muscular tissues (of uterus, alimentary canal, etc.), which it induces.

Symptoms.—The more acute cases present many of the characters of severe gastro-enteritis, vomiting, purging, abdominal cramps, with mental dulness and depression, causing death with convulsions within two or three days. In other cases, marked by a slower onset and progress, the limbs, and perhaps even the trunk, are the seat of symmetrical dry gangrene, frequently accompanied by the most excruciating pain, though not invariably so. Or both forms may coexist. In milder cases, where a less virulent dose of poison has been taken, there may be merely anæsthesia of the extremities, spasms of the legs, with heaviness and depression of spirits. Such symptoms closely resemble the trophoneuroses known as Raynaud's disease, erythromelalgia, etc., some of the recorded cases of which appear to have been mistaken for ergotism.

Sclerosis of the posterior columns and posterior root zones of the spinal cord has been detected.

No **treatment** has hitherto been of any avail.

PELLAGRA is a non-febrile disease which prevails in Italy, Southern France, Roumania, and Egypt, due to the consumption of maize which has become mouldy. Like other maladies of the kind it is predisposed to by poverty, exposure, alcoholism, syphilis, and other constitutional affections. It is more commonly met with in adults, but is not restricted to any age or either sex.

The essential **symptoms** of the disease, apart from those determined by the associated conditions, are connected with the digestive, cutaneous, and cerebro-spinal nervous systems.

Often commencing with dyspepsia, abdominal pain, diarrhœa or constipation, and thirst, the tongue becomes characteristically denuded, and occasionally the parotid glands painlessly swollen

(Dr. Sandwith). The general nutrition suffers, and patients emaciate considerably.

The skin eruption at first resembles severe sunburn, followed by desquamation and patches of roughening, which may be of considerable thickness on the hands, forearms, feet, legs, shoulders, neck and face, that is, on the exposed parts. The eruption may be accompanied by burning and itching, and later the skin becomes atrophied and wrinkled, and in places anæsthetic. Occasionally bullæ, followed by chronic ulcers, are observed. The cutaneous manifestations tend to recur annually, especially in the spring, perhaps determined thereto by the sun. The more important nervous symptoms are pain in the back, often very severe, with tenderness on pressure, exaggerated knee-jerks and a tendency to increase of other reflexes, marked insomnia, convulsions, spastic paralysis of the lower extremities, unilateral ptosis and mental depression, deepening into melancholia or dementia, or occasionally mania.

The duration of the disease is uncertain, but is usually two to three years. The mortality is largely attributable to concurrent diseases, of which parasitic worms (especially the *Bilharzia* and *Ankylostoma*) are the most serious in Egypt. The only characteristic lesion found post-mortem is sclerosis of the posterior columns and pyramidal tracts of the cord in the cervical and dorsal regions.

Treatment.—The disease is more easily prevented than cured; only the best maize should be eaten, and it is well not to subsist exclusively on that cereal. Rest, tonics, good food, and attention to any associated maladies are essential.

LATHYRISM is the name given to a malady formerly not infrequent in Southern Europe, but now almost only met with in India and in times of famine, caused by an undue admixture with flour of the seeds of certain species of vetch, *Lathyrus sativus* and *L. cicera*. The associated bad hygienic conditions under which those exposed to this disease exist largely contribute to its occurrence.

The **symptoms** are mainly those of a sensori-motor character affecting the legs—a peculiar paraplegia, often of quite sudden onset, with pain in the back and loins, and sometimes preceded by tremor, in which the hands may be involved. Great difficulty is experienced in rising from the sitting posture, which is assumed with facility. The knee-jerks are increased, and the sphincters are unaffected. Great variability has been noted in regard to cutaneous sensation, which may be unimpaired or exhibit all degrees of increase, diminution, or perversion. There is no fever, but the wasting of the legs is considerable and often unequal.

The exact lesion, presumably in the spinal cord, has not yet been described.

Treatment.—Some benefit has followed on change of diet and improved hygiene, but owing to the difficulty of overcoming native prejudices cure is seldom complete.

ALCOHOL

The variations in degree and in character of the toxic manifestations of alcohol depend not only on the dose of the poison and form in which it is administered, but also upon many circumstances connected with the individual. Chief among these are hereditary predisposition, and an unstable nervous system, inherent or acquired, which favours the development of neuroses, and especially a craving for intoxicants; the habit of taking alcoholic liquors, whether in moderation or excess; the state of health, amount of food, mental anxiety or overwork, constant pain, occupation, etc. Some of these indeed, besides qualifying the effects, may be regarded as etiological factors.

Clinical characters of alcoholism.—These readily fall into two groups—those connected with a single excessive dose, and those resulting from a prolonged course of immoderate drinking.

In ACUTE ALCOHOLISM the symptoms necessarily vary from those of a slight mental exaltation to a profound coma. It is upon the nervous and neuro-muscular systems that the poison produces its chief effects, its action on the brain showing all gradations of stimulation, over-action, depression, inhibited action and narcosis, as the higher cerebral centres, the cerebellum, the spinal cord, and medullary centres are successively affected; and unless the dose prove fatal the results are transitory, passing off and leaving no subsequent effects, except perhaps headache, which would appear to be due in great measure to the liquors being ill fermented, or containing other noxious ingredients, or to be connected with dyspeptic disturbances, determined by the direct effect of the fluid taken upon the stomach and its contents. In the earlier stages the mental faculties are temporarily sharpened, later to be followed by an obscuration of intellect, deepening into drowsiness and heavy sleep; the volubility gives place to thickened, incoherent speech, and the oftentimes heightened muscular activity to inco-ordinate movements, usually first noticeable in the legs. The face is flushed, the eye, at first bright, becomes dimmed and heavy as the individual lapses into a state of unconsciousness, from which it is difficult to arouse him, until he

has slept off the poisonous effects of his excess. Should, however, the amount taken have reached fatal limits, the narcotic effect is rapidly reached, and with increasing coma the skin becomes cold and clammy; the pulse, at first full, becomes small and scarcely perceptible; the pupils insensible to light, and dilated or contracted; respiration stertorous; muscular twitchings occur and may pass into general convulsions; and the patient dies, perhaps delirious, with a high temperature or in a state of syncope.

DELIRIUM TREMENS is the name given to a peculiar condition which occasionally follows a heavy bout of drinking, but far more commonly supervenes in a chronic alcoholic subject, excited by some injury or operation, or by an attack of acute illness, such as pneumonia. One of the earliest symptoms noted is a dislike for alcoholic liquors, and a consequent cessation of drinking. The patient quickly becomes restless, with very disturbed sleep, which soon passes into insomnia; he talks incessantly, passing from one subject to another, and, though usually answering a question fairly sensibly, quickly relapses into his inconsequent chatter. He is the subject of all kinds of hallucinations and illusions, fancying himself to be injured, which may lead him to acts of violence, and perpetually imagining that he sees insects, rats, and other animals crawling over the bed or about the room. There is a marked and constant muscular tremor, affecting not only the limbs, but also the tongue and lips, thereby rendering articulation indistinct. The tongue is furred, later dry and brown, and the breath is offensive. The bowels are confined, and whilst the appetite is generally lost and all food is refused, there is considerable thirst. Other febrile symptoms accompany the pyrexia, which may be considerable, such as flushed face and suffused eyes, sweating, high-coloured, scanty urine containing a trace of albumen, with quick, soft, rapid pulse and hurried respiration. This condition, if untreated, usually lasts three or four days, when the patient, who has by this time become obviously weaker, gradually falls into a heavy sleep, from which he may awake considerably better as regards his mental state, though still very weak, or it may be that the improvement does not set in until the sleep has been repeated. In some cases, however, especially if there be pneumonia or the general health be gravely impaired, the patient, instead of improving, gradually sinks into a state of extreme prostration, with low, muttering delirium, a small flickering pulse, and dies from syncope or in convulsions.

The symptoms of CHRONIC ALCOHOLISM are altogether of a milder and more insidious character, though tending to a fatal termination from the serious structural changes induced in important

organs. No statement can be made respecting the amount of alcohol or the time required to bring about these changes; the personal tolerance, the form of liquor, and the circumstances of the individual combine to produce the greatest variation. Nor is it easy to say exactly when the symptoms commence, nor indeed to discriminate those which are characteristic, but in the majority of cases dyspeptic disturbances are among the earliest signs, especially anorexia, more particularly for breakfast; a foul tongue and morning retching and vomiting of mucus with considerable coughing and expectoration; diarrhœa, continuous or varied with constipation. Yet these signs may be insignificant in degree, and there is as often to be met with a general failure of health with diminished capability for work, mental or physical, and an alteration in disposition towards being morose or irritable, which later attains to distinct perversion of the moral sense, the patients becoming untruthful and deceitful, particularly in regard to their drinking habits and the means for the gratification of the same; and it may be noted that whilst men will, as a rule, on pressure, confess to the vice, women rarely or never do. Along with this general sense of illness, intensified by broken, unrefreshing sleep, or even insomnia, there is a widespread muscular tremor, at first controllable, but later called forth by the slightest effort and quite beyond the patient's power of restraint; hands, arms and legs, tongue and lips alike show it in varying degree. This tremulousness may at times amount to grosser "startings" and "tremblings," showing the unbalanced state of the nerve centres. Sooner or later evidences of hepatic and possibly renal disease may become manifest, indeed a palpable liver may be the first indication to the physician of what is wrong, for it may be taken as a clinical fact that the liver of an adult should not be apparent to the touch, and if it be so that it is certainly too hard and possibly too large. As the cirrhosis becomes established conditions due to it are developed and will be described when that disease is considered. The enlarged liver is sometimes due to congestion from the heart weakness rather than to fibrotic changes. Chronic interstitial nephritis is set up in perhaps a quarter of the cases, and in a smaller proportion the renal changes result in the production of the "large white kidney." Very different are the appearances presented by chronic alcoholics; whilst many—perhaps the majority—have a puffy and bloated expression, with blotchy, pimply face and suffused and watery eyes, and yellowness of conjunctivæ, others may look lean and sallow, with soft, waxy shrivelled skin. Obesity prevails among beer drinkers independently of the amount

of food consumed, and especially among females and those leading sedentary lives. In others there is a slow but continuous wasting, especially of the legs, to which the abdomen, when ascitic from portal obstruction, may offer a striking contrast. The ill-nourished skin is apt to become eczematous, and such cutaneous eruptions as break out are singularly intractable. And thus may the drinker go on for months or even years, now better, now worse, as his opportunities or means permit of a greater or less consumption of liquor. But his progress, unless the evil habit be discarded, is surely downwards; the appetite, seldom good, becomes worse, the food is ill-digested, the general nutrition increasingly suffers, and the heart, which has tended to fail, gradually becomes weaker, as bronchitis, rarely absent in some measure, adds a further difficulty, which may of itself be sufficient to cause death. Or a fatal termination may be more directly attributable to hepatic or renal disease, or to the vascular degeneration or other "gouty" manifestations which the alcohol has induced. In another class of case, in which many of the above symptoms are entirely wanting, evidences of more serious involvement of the nervous system are present, less often in those who drink beer than when other spirituous liquors are consumed, and far more frequently in women than in men. These are the signs of multiple neuritis, chiefly affecting the limbs, though by no means limited to them, the vagus and phrenic having been found to be implicated, to which circumstance the respiratory and cardiac troubles may in part be attributed, as well as the almost sudden deaths which sometimes occur in these cases. The symptoms of neuritis will be more fully treated subsequently; here it will suffice to mention the pains in the limbs, tenderness along the nerve trunks, anæsthesia or perverted sensations, diminished reflexes, and wasting, with loss of muscular power up to complete paraplegia. The damage to the cerebral and spinal tissues is much less marked, and although certain paralytic conditions may be attributable to changes in these organs, it is to the neuritis that the symptoms are mainly due. The mental and moral aberrations already alluded to may reach an extreme degree, and various forms of insanity may originate from chronic alcoholism. But it is doubtful whether its abuse is responsible for this last condition so often as is supposed, especially in the case of general paralysis of the insane.

The **differential diagnosis** of acute alcoholic poisoning, from the coma of uræmia, diabetes, and other toxic conditions, from cerebral hæmorrhage or from post-epileptic states; of delirium tremens from meningitis or mania, or the delirium of certain

infective fevers ; of chronic alcoholism from general paralysis of the insane in its earlier stages, is first of all to be based upon a history of drinking which is not always easy to obtain. The symptomatic details will be referred to in the account of these several diseases.

The **prognosis** in the acute forms of alcoholism has been incidentally mentioned ; in the chronic state it is often difficult to say the exact line beyond which recovery is impossible, provided that drinking be entirely given up. It is remarkable, however, how very quickly some improvement of the subjective symptoms will follow a cessation of the habit, and even when there is reason to believe that obvious structural changes have taken place in liver, heart, or nerves, some degree of recovery may be looked for. The development of epileptoid convulsions, or of insanity, is well-nigh hopeless. The great liability of the individual to relapse to his former habits makes a thoroughly good prognosis very doubtful.

Morbid Anatomy.—There is nothing distinctive in the post-mortem appearances of death from acute alcoholic poisoning. Signs of gastric irritation, even to erosion of the mucous membrane, may be present, and the entire alimentary canal may be in a state of extreme hyperæmia ; but this is not constant. The lungs and sometimes the brain may exhibit a similar condition. Nor in fatal cases of delirium tremens are there any special appearances beyond those due to chronic alcoholism, upon which this state usually supervenes.

In chronic alcoholic poisoning, however, the resulting tissue changes are in a great measure characteristic, at least of the class of poisons to which alcohol belongs, including such as arsenic, lead, antimony, and in some degree phosphorus. Long repeated ingestion of alcoholic liquors inevitably leads to changes in most of the organs of the body, though these changes vary in great measure with the character of the liquor, whether spirituous or malted, as also with the degree of concentration in which it is taken, and especially on the quantity of food that is consumed by the drinker. Some share also in the result must be attributed to the tissue susceptibilities and idiosyncrasies of the individual, for very diverse appearances occur in different persons who may be pursuing apparently the same excesses in the same way.

Briefly, the structural effects of chronic alcoholism are : (a) Those of a degenerative or necrotic character, as met with—(i.) in the epithelial cells, more particularly of the gastric mucosa and of the liver, and in a less degree of the kidneys, respiratory tract, and skin ; (ii.) in the peripheral nerve fibres, but scarcely at all in the brain and spinal cord ; (iii.) in the muscular fibres of the heart and

systemic muscles, though here the changes may be in part trophic, induced by the nerve lesions.

(β) A new formation of fibrous tissue—fibrosis—resulting from a chronic change in the connective tissue stroma, especially of the liver, nerve fibres, kidneys, and gastric mucosa.

(γ) An over-development of the adipose tissue, subcutaneous and sub-serous, due to a diminished oxidation in the ultimate tissue elements, determined by the poison.

The grosser lesions which these tissue changes entail are manifest in the *liver*, which exhibits all degrees of fibrosis, with varying preponderance of fatty change in the hepatic cells, whereby the so-called hypertrophic and atrophic forms of cirrhosis are determined; or the viscus may be in an advanced stage of fatty degeneration, with but little interstitial overgrowth, or much congested from cardiac failure. The *kidneys*, though often enlarged from hypertrophy, and sometimes “granular” and fibrotic, are far less commonly and extensively involved than the liver. The *stomach* is frequently in a state of chronic catarrh, with fibroid thickening of the mucosa and submucosa, or the organ may be dilated (as in beer drinkers) and the walls thinned. The *intestines* are sometimes injected, but oftener no change is apparent, whilst the *pharynx* is usually much congested. *Hæmorrhoids* and gastro-æsoophageal varices are frequently met with as a result of the portal obstruction in the cirrhotic liver, though the former are probably less dependent on this condition than was formerly thought. The *heart* is both dilated and hypertrophied, the fibres degenerated with interstitial myocarditis; the valves are apt to be thickened and involved in the atheromatous degeneration which spreads from the *aorta*; and the *arterioles* are fibrotic. There is frequently *chronic laryngitis* with *bronchitis* in the larger tubes, and the association of *tuberculous phthisis* with alcoholic cirrhosis of the liver is well established, the course of the disease being usually one of rapid caseation and excavation with broncho-pneumonia, and rarely towards fibrosis. Impairment of the trophic influence, owing to vagal degeneration, has been suggested as favouring the incidence of tuberculosis and its distinctive character. Gangrene of the lung has also been observed, and a remarkable condition of denudation of the extremities of the bronchial tubes, which are found to contain large accumulations of mucus, the explanation, probably, of the copious morning expectoration so often occurring in alcoholics. The *testes* have been found atrophied, and the ovaries fibrosed, but these are certainly not constant or even common changes. The *skin*

of the face is often congested with dilated venules and a varying degree of acne rosacea ; elsewhere the skin is coarse and greasy, or pale, soft, atrophied, and wrinkled. *Obesity* or extreme *emaciation* are equally met with.

The naked-eye appearances seen post mortem in the organs of the *nervous system* are limited to the *brain*, which is atrophied, with consequent thickening and opacity of the pia mater and arachnoid, enlarged pacchionian bodies, and considerable excess of subarachnoid fluid ; the sulci are deepened and the brain substance firm, similar appearances being met with in advanced age. Evidences of meningitis are rare. It is the microscopic changes, however, which are of the most importance. For the most part these are restricted to the nerves, although patches of degeneration and sclerosis have been noted in the brain and *spinal cord*, probably by extension from the meninges, as well as sclerosis of the posterior tracts ; and occasionally degeneration or deep pigmentation in the nerve cells, secondary to the changes in the peripheral nerves. The alterations in the *nerves* chiefly affect the peripheral branches, though the main trunks and even the plexuses may be involved. Nor are the spinal nerves alone implicated, for the vagus at least among the cerebral has been found affected. The component parts of the nerve are affected differently ; the fibre itself exhibits degenerative changes, the myelin sheath being broken up into masses, the axis cylinder becoming granular and finally disappearing with the myelin, the fibre being ultimately represented by a finely granular and pigmented débris ; the nerve sheath and its prolongations, however, manifest an inflammatory condition, becoming infiltrated with leucocytes and later a fibroid overgrowth. The relative proportion of these parenchymatous and interstitial changes varies generally, and there are usually to be seen isolated nerve fibres quite unchanged. The similarity of these structural alterations in the *nervous tissues* to what is met with in chronic lead or arsenical poisoning or certain microbic intoxications, as diphtheria, is noteworthy.

Treatment.—Unless the dose taken be sufficient to induce a state approaching coma, nothing need be done, and the patient may be allowed to sleep it off, especially if he have vomited. But it may be necessary to wash the stomach out, and perhaps desirable to rouse him by the shock of an electric battery. Should collapse threaten, hot bottles and warm stimulant drinks, or even ether or strychnine subcutaneously may be required.

The management of the chronic alcoholic is far more difficult.

Absolute deprivation of alcohol in any form should be at once insisted on, but this can seldom be satisfactorily carried out unless the patient voluntarily submit to the restraint of a well-regulated institution, and, better still, under the Inebriates Act (1888). Supposing this to be accomplished, much of the difficulty is overcome, at least for the time. The withdrawal of the poison will of itself do much, and for the rest reliance must be placed on good food, fresh air, and especially mental and physical occupation. The diet must be regulated according to the patient's digestive capability, which may be assisted by the mineral acids, alkalies, vegetable bitters, and pepsin. The bowels should be regulated and gastro-intestinal catarrh treated by bismuth and hydrocyanic acid. It is all-important to obtain sleep, and for this hypnotics may be necessary, and the less depressing ones should be chosen, such as sulphonal or trional. Morphia or opium should be given with the greatest care, and not at all if the urine be albuminous. Their effect should be watched, and an ample interval allowed before a second dose is administered, and this specially applies to the giving of such drugs in delirium tremens, when the natural tendency of the disease is to the onset of sleep after three or four days, and when soporifics have as a rule very little effect even in full doses. The bromides in combination, with or without hyoscyamus or opium, are often useful. Cold packing is in many cases an excellent sedative. Too much stress cannot be laid on the necessity there is for feeding such patients, and every effort must be made to effect this; milk, milk and egg, thinly-made Benger's food are the most suitable. The subject of delirium tremens, unless extremely violent, can generally be managed by firmness and without mechanical restraint, which is only sometimes necessary, provided there be ample assistance at hand. It must be remembered that such patients, in consequence of their delusions, may commit all kinds of acts harmful to themselves as well as others, and they should never be left for a moment.

OPIUM—MORPHIA

The various preparations of opium chiefly owe their deleterious effects to the alkaloid morphia, which is a typically narcotic poison. As with other drugs of this class, individual susceptibility to its effects varies considerably, and is specially conditioned by age, habit, and, when taken by the mouth, by the absorptive power.

ACUTE OPIUM POISONING—Symptoms.—After a lethal dose

there may be some slight and transient excitement, followed by drowsiness and sleep, which gradually deepens into the most profound coma, with loud, stertorous, and slow breathing. The pupils are contracted, the skin moist and sweating, there is profound anæsthesia, and the respiration becomes gradually slower and slower, the complexion of the patient appearing ashen, with dusky, cyanotic lips. The pulse, at first quick, is later feeble and irregular. The bowels are constipated and the urine is scanty. Death takes place after some hours, and is due to failure of the respiratory centre producing asphyxia, and may be immediately preceded by slight convulsive movements and dilatation of the pupils. The post-mortem signs are those of asphyxia, with the addition, possibly, of a smell of opium.

Between a mere condition of sleepiness, from which the patient may be roused, and the state of profound coma above described, there are necessarily all degrees.

The **diagnosis** of opium poisoning from conditions which resemble it is often difficult. The pin-point pupils combined with coma are very characteristic, but it must be remembered that pin-point pupils are found also in poisoning with carbolic acid, physostigma and pilocarpine, as well as in cases of hæmorrhage into the pons, and in sufferers from locomotor ataxia. Coma again is common in cerebral hæmorrhage, Bright's disease, and diabetes. An examination of the urine both for albumen and sugar should be made, and the presence or absence of definite paralyses or the occurrence of convulsions must be determined. The smell of the breath, whether urinous, or acetonous, or alcoholic, or laden with carbolic acid or opium, will often give a clue. The possibility of a combined state, as of an overdose of morphia in a uræmic subject, should be remembered.

Treatment.—If the dose has been taken into the stomach, the stomach must be promptly and repeatedly washed out, and for this it is advisable to use a weak solution of potassium permanganate (30 grs. to the pint), which is said so to affect the alkaloid as to render it harmless. This should be continued until the pink colour is no longer destroyed by passing through the stomach. In the state of profound coma which usually exists all emetics are uncertain in their action. The patient must if possible be roused by the battery or other means, and kept awake with doses of hot coffee, and be kept walking to and fro.

It must be remembered that narcosis from opium is very liable to relapse, and that a patient who has taken a large dose is not to

be considered as out of danger for at least twenty-four hours after apparent recovery from the first effects.

In poisoning with opium it is recommended that subcutaneous injections of liquor atropinæ sulphatis should be given. There is some evidence that the action of atropine is antagonistic to that of morphine, and many cases have been published which apparently show that the results of giving atropine have been beneficial. The antagonism of these two alkaloids is not complete at all points, and it is most important that the doses of atropine administered be kept strictly within ordinary therapeutic limits. The effect must be closely watched, and not more than 2 minims of the solution should be administered at intervals of an hour. Caffeine in 5 grain doses has been successfully employed to counteract the cardiac depression, and hypodermic injections of liquor strychninæ hydrochloratis may be used with a like object.

It need hardly be said that when in poisoning by morphia the respiration becomes very slow artificial respiration should be practised and continued with some persistence.

CHRONIC OPIUM POISONING—MORPHINISM.—This condition not infrequently supervenes on a course of medicinal treatment, after the legitimate necessity for the drug has passed away. The soothing or even slightly stimulant effects which contribute so much to the sense of well-being of the individual—and for which opium in Eastern countries has well-nigh become a necessary of life—are so acceptable that indulgence in the habit grows until it leads to a confirmed deterioration of health.

The subjects of morphinism are generally neurotic, often the victims of painful chronic disease, or they are persons over-immersed in business or affairs who have overtaxed their nervous energies, and becoming restless and sleepless have resorted to morphia for relief. Sometimes they have been overtaxed by the calls of "Society"; sometimes there is a skeleton in the closet, such as the inevitably approaching bankruptcy of the seemingly successful man, a fact known only to himself; sometimes it is a philanthropic or other object which the patient is pursuing with a fervour which is scarcely sane, and he pours from his platform eloquent exaggerations which are bred of drugs or stimulants.

The mode in which the drug is taken varies with inclination and opportunity. Several ounces (even 8 or 10) of laudanum may be consumed daily, or the crude opium may be swallowed in the form of pills, or smoked, or solutions of morphia may be subcutaneously injected.

Action and reaction are equal and contrary; the stimulating effects are followed by inevitable depressions, and as the trough of the wave bears a gradually increasing proportion to the crest, the stimulant has to be administered with increasing frequency or in increasing quantities. The morphinist at last is only fit for business when he is under the influence of the drug; when the effect has passed off he is "fit for nothing." It is well known that the quantity of opium, or laudanum, or morphia which a morphinist will learn to tolerate is prodigious. The equivalent of 10 or 12 grains of morphine *per diem* administered hypodermically is easily reached, and five or six times this amount has been taken.

Symptoms.—How is the morphinist to be detected; by what signs is he known? Variability of temper, oddness of manner, and unreliability often receive their explanation by the discovery of the "morphia habit." Dr. Clifford Allbutt rightly lays great stress upon unpunctuality and the not keeping of appointments as an indication which often leads to the detection of the true cause.

The morphinist may have a contracted pupil and a peculiar sallow, muddy complexion. The muscles may be flabby, the nutrition bad, the appetite capricious and digestion poor. Diarrhœa is a frequent complaint, though constipation is the rule. The secretions generally are much diminished, except the sweat, which may be excessive. Later, severe epigastric pain is frequently complained of. The patient may become the subject of hallucinations, or even of delirium with considerable tremor, thus resembling the alcoholic. The increasingly deteriorated health favours the occurrence of pulmonary or other disease, to which the morphinist finally succumbs, or death may be sudden from heart failure. Such patients should always be stripped and carefully examined on the arms, trunk, and legs for the needle pricks of the hypodermic syringe.

The chronic drunkard being, in this country, by no means uncommon is more easily recognised than the morphinist. The two are often not very different in respect of character and social habits, though the former is generally the more degraded and unkempt, and crumpled finery with muddy skirts is very characteristic of the lady drunkard.

The **treatment** of this condition, as of alcoholism, is not very easy, and demands the exercise of a good deal of judgment. It is impossible to do any good to the patients unless one can obtain absolute control over them, and if possible they should be placed under medical surveillance in a suitable "Home." Half measures

and the substitution of milder doses for the stronger seldom result in any benefit. The promises of the patient are worthless, the cravings for the narcotic, as for drink, being quite irresistible. In extreme cases, when the drug is withdrawn, the patient may need careful watching. Sudden and complete withdrawal of the drug is seldom advisable, owing to the exhaustion and diarrhoea, vomiting and delirium, that are likely to supervene with alarming severity. The quantity and frequency of administration should be gradually diminished over some days, varying with the daily amount taken and the state of the patient. The hypodermic injection may be increasingly diluted until it consists almost or entirely of plain water. In consequence of dyspepsia and anorexia it may be very difficult for a few days to administer food, and if the patient have a fatty heart he may die from collapse. Dyspepsia must be treated on ordinary lines, and fluid nourishment, peptonised or otherwise, must be administered by mouth or rectum. If it is found necessary to administer alcoholic stimulants or narcotics because of the danger of collapse from complete withdrawal, they should always be given in an unaccustomed form and without the knowledge of the patient. The bromides with caffeine are the most suitable, but their administration is seldom necessary after the first few days. To counteract the cardiac depression and small feeble pulse, trinitrin and spartein have been recommended.

In the general management of the patient moral control should take a prominent place. Firmness, untainted by maudlin sentimentality, is necessary. In order to improve their nutrition muscular work in the open air is necessary for all these patients, and it is difficult to devise muscular work which at the same time interests the mind. Games of all kinds should be provided, but games are apt to pall when ordered as a therapeutic measure, and the daily walking or cycling for a stated period or a stated distance becomes, in time, almost as irksome as the treadmill. Games and aimless pursuits should be relegated to the intervals of work, and the patients should be taught that an unproductive life, unless dignified by labour of some kind, is ignoble. These unhappy people are often credited with "talents," and if that be the case they must be evoked. Every inmate of a home ought to contribute to the common weal. It is the aimlessness of conventional society which is answerable for much of the drugging and drunkenness of the present day, and it is but too plain that even the "philanthropic" denouncing of your neighbours is no substitute for honest work which has tangible results.

The studio, the library, the music-room, the schoolroom, the workroom, the kitchen, the dairy, the laundry, the carpenter's shop, the garden, and the farm ought to provide a sufficiency of real productive work. In inebriate "Homes" and similar institutions the unproductive drone ought to be at the bottom of the social ladder.

Among other intoxicants that are habitually taken for the excitement they produce may be mentioned ETHER, several ounces of which may be daily consumed by one who is accustomed to the drug. Its effects resemble those of alcohol, but are somewhat more violent and also more transient in duration. A chronic gastritis, with indigestion, debility and wasting with nervous weakness, are the chief symptoms resulting from a prolonged use of the stimulant.

COCAINISM appears to be increasingly prevalent, the drug being either taken originally as a substitute for morphia, the patient contracting in exchange the cocaine habit, or its use is gradually acquired, after its beneficial tonic effects have been once experienced. It is chiefly for the relief of the sense of exhaustion and fatigue and consequent exhilaration that cocaine is indulged in, and increasing doses becoming necessary, a habit as serious as morphinism is quickly contracted. Taken chiefly by the mouth, though not infrequently by subcutaneous injection, as much as 30 grains and more have been consumed within twenty-four hours. The symptoms are similar to those presented by the morphinist, emaciation, muscular and mental enfeeblement, insomnia, tremor, and dyspeptic symptoms such as nausea, loss of appetite, and diarrhoea. In many respects the cocaineist is worse off than the morphinist, and the effective treatment by isolation, withdrawal of the drug, careful feeding, and massage is even more difficult of attainment.

METALLIC POISONS

The members of this group which are more commonly met with as the cause of poisoning are phosphorus, mercury, arsenic, lead, and much less frequently antimony, copper, and zinc, the two last especially among brass workers. For an account of the symptoms following single or fatal doses and their treatment, reference must be made to works on toxicology; here will be described the conditions of ill-health which follow the long-continued absorption of small doses, whether administered designedly or accidentally

in the course of various trades in which these substances are employed.

It may, however, be mentioned that all appear to have a specific effect upon the alimentary tract, and even when applied externally some may produce intestinal irritation and diarrhœa. When mercury is administered by inunction or is used as a vaginal douche, symptoms of intense dysentery have often supervened, and there can be no doubt that the large intestine is an important, probably the most important, channel for the elimination of many metallic poisons. This is borne out by the evidence from many post-mortem examinations, of which it has been recorded that whereas the stomach and duodenum have presented the appearance of inflammatory reaction and hæmorrhage, the result of the direct contact of the irritant, the small intestine below the duodenum has afforded no such evidence; whilst the large intestine and rectum are often intensely inflamed, and in the case of mercurial poisoning may be the only part of the intestinal tract which is so affected. This is a point of great practical and scientific interest.

PHOSPHORUS is capable of acting as a poison of great potency. The common yellow phosphorus is alone poisonous, the allotropic modification (or red phosphorus) has no such dangerous properties. The cases of acute phosphorus poisoning are usually accidental or suicidal. It may be taken in the form of match-heads or as "phosphorus paste," a preparation extensively sold for the destruction of black beetles and rats. Phosphorus, when swallowed in the form of "stick" (as it is generally sold), is said to be less dangerous than in a finely-divided condition. Phosphorus which fumes in the air at ordinary temperatures is soluble in oils and ether.

Symptoms.—When phosphorus paste is swallowed there is usually more or less gastric irritation within half an hour or so, pain in the abdomen with nausea and vomiting of altered blood. The breath may be luminous in the dark, and has the characteristic garlicky odour of phosphorus.

If the patient be seen early the phosphorus may be removed from the stomach before absorption has taken place and no further evil effects result. This, however, is rarely the case, and the practitioner needs to be warned that after the primary symptoms of gastric irritation subside there is a lull for three or four days before the constitutional symptoms, which constitute the real signs of danger, manifest themselves. There is usually general discomfort, with a sense of pain and weight over the liver, accompanied by

jaundice, a feeble pulse, and gradually increasing weakness with headache and insomnia. The urine is generally scanty, sometimes slightly albuminous, with bile pigment and a marked deficiency of urea. In a case observed by the writer there was sugar (which is rare) and a copious deposit of stellar crystals of uric acid; there may be leucin and tyrosin. There is rarely a rise of temperature in these cases. The liver is large at first and is tender and painful, but in some cases it atrophies subsequently. Low muttering delirium comes on; the patient becomes comatose and usually dies from heart failure within a week or ten days of taking the fatal dose of phosphorus. There may be petechiæ and subcutaneous hæmorrhages, bleeding from the gums, and occasionally discharge of blood from the kidneys, bowel or vagina. It is said that in cases of phosphorus poisoning a leech bite has been known to give rise to uncontrollable hæmorrhage.

Morbid Anatomy.—Post-mortem there is evidence of extensive fatty degeneration of all the tissues. The liver is bright yellow and may be large or small. The heart muscle and kidneys are obviously fatty, and the tendency to hæmorrhage is probably to be accounted for by fatty changes in the wall of the blood-vessels.

These cases are indistinguishable except by their history from that rare condition which is known as acute yellow atrophy of the liver, and in all cases where the latter diagnosis is made it is most important that phosphorus as a cause be excluded, and the practitioner must remember that in cases of attempted suicide patients are naturally reticent.

Treatment.—If the case be seen early turpentine in half-drachm doses should be administered at once, and the stomach should be washed out without delay. If jaundice has set in the prognosis is in all cases very bad, and although turpentine may be given, its power for good at this stage of the trouble is open to question.

Chronic phosphorus poisoning, sometimes termed “phosphorism,” is commonly met with among lucifer match-makers, who are constantly exposed to the phosphorus fumes. In this way a condition of general ill-health is established, marked by anæmia, a yellowness of skin, albuminuria, and brittleness of bones, the poison being found in the urine and tainting the breath. More serious is the so-called “phossy jaw,” a form of osteomyelitis and necrosis which follows on a gingivitis, and apparently favoured in its occurrence by the presence of decayed teeth. The lower jaw is principally or only affected.

Prevention by the use of red phosphorus, good ventilation of

the workshops, cleanliness, and medical inspection of the workers, particularly as regards the teeth, is of paramount importance. The treatment of the condition, when established, consists in removal from the occupation, a milk diet, small doses of turpentine, and surgical attention to the local mischief.

ARSENIC is well known and widely used, especially in chronic skin diseases and in chronic diseases of the nervous system. It is said to increase the feeling of *bien être*, and in some countries it is employed as an aphrodisiac. It certainly improves the coats of both dogs and horses, and it also enjoys a reputation as an "anti-periodic" in countries where malarious fevers are common.

Symptoms.—Although there is good evidence to show that a certain amount of toleration for arsenic may be established (as among the arsenic eaters of Styria), it is nevertheless true that those who take arsenic medicinally for long periods or who are otherwise exposed to its effects by their employment, or by the use of arsenical wall-papers or pigments, are liable to suffer in a variety of ways. Artisans who are employed in workshops where arsenical dust is liable to be present are apt to manifest local cutaneous inflammations of an eczematous type, due to direct irritation of the dust. Such affections are prone to occur in warm and moist situations, as in the folds of the axillæ, between the thighs and the scrotum, and round the margins of the nostrils and eyes. Symptoms of gastro-enteritis are more or less constantly present; the general health is impaired; the patient becomes anæmic and emaciates, and muscular cramps are frequently complained of. Frontal headache is another common result of prolonged exposure to arsenic, and occasionally there may result pigmentation of the skin, thickening of the integuments, especially of the palms and soles, and a symmetrical peripheral neuritis, accompanied by the sensory and paralytic phenomena which are characteristic of that condition. A smarting of the eyes and a dry soreness of the fauces, with the sensation of a hair in the throat, causing constant hawking, are symptoms frequently complained of.

It is sometimes not easy to detect the source of chronic arsenical poisoning when such may be suspected. Wall-papers and other fabrics which are printed in gay colours must always be objects of suspicion, and it must be remembered that, although pigments may be stated to be "non-arsenical," the oxydising power of arsenic acid is occasionally made use of in developing the tints of aniline dye. Some years ago a large number of persons who wore a particular brand of "magenta" coloured socks suffered from eczematous

eruptions of the legs, and this was found to be due to the use of arsenic for this purpose.

The **morbid changes** in the organs induced by the long-continued ingestion of arsenic are an inflammation of the gastrointestinal mucosa and fatty degeneration of the epithelia of the canal, as well as of the liver and kidneys, induced apparently during the elimination of the poison by these channels, irrespective of its mode of entrance into the body. The systemic muscles exhibit a similar change.

The **treatment** of the condition is comprised in removal of the cause, a bland unirritating diet, iodide of potassium in small doses, and the appropriate treatment of neuritis by massage and strychnine, and if necessary sedative applications.

CHRONIC MERCURIAL POISONING is very rare in this country, where the use of mercurial preparations in the arts is tending to decrease.

Symptoms.—Salivation, ulceration of the buccal mucosa, and dysentery are the symptoms which are liable to occur in patients who are undergoing a course of mercurial treatment, and it must be remembered that such symptoms are very prone to appear in patients who have gouty kidneys or are tainted with scurvy. The worker in mercury is liable to suffer from mercurial tremor of the hands or feet or "the trembles," as the condition is usually called by the artisans. The tremor is coarse in character, of considerable range, and may be so severe as to prevent the patient from feeding himself or from walking. It is, though liable to become constant, mainly an "inattention"¹ tremor, *i.e.* it is developed by the attempt to use the affected limbs. Anæmia, emaciation, with œdema of the feet, and great weakness and pain in the muscles develop in proportion to the continuance of exposure to the poison, however it may be absorbed.

Treatment.—Tonics and such food as is found to be digested should be administered. The dysenteric symptoms may require opium, bismuth in a solid form, or rectal astringent injections; and a mouth wash of potassium chlorate should be used frequently for the salivation and ulceration of the mouth.

CHRONIC LEAD POISONING is of great practical importance and is still common among lead workers—plumbers, painters, potters (owing to the glazes used), and the manufacturers of "white lead." Various articles of food may be contaminated and give rise to

¹ The term "attention," as suggested by my colleague Dr. B. Abrahams, would seem to express more correctly the nature of these tremors.

poisonous symptoms, which may affect a number of people in an epidemic form, and the real cause, or the channel of conveyance being unsuspected, the malady may continue for considerable periods. Water is a frequent source of lead poisoning, especially water which contains traces of vegetable acids or other organic matter, such as that collected from peaty soils or that is stored in leaden cisterns and pipes. Boiling does not diminish its noxious character. Similarly the beer left all night in the leaden pipes in public-houses is a cause of poisoning among potmen and others. Food may also be impregnated by the wrappings, tins, etc., in which it may be supplied, or even by cooking utensils. Articles of diet are occasionally adulterated with lead salts, the chromate is used for colouring cakes, and litharge added to wines to diminish acidity and harshness. Among less common sources are the leaden pads used by file cutters and leather cutters, the constant handling of type, bullets, and shot; and one not to be overlooked—hair dyes. Serious symptoms have followed the medicinal administration of lead, both internally and as lotions, and also its use as an abortifacient.

From these illustrations, it will be seen that the poison gains entrance to the system chiefly by the alimentary canal, and then most frequently owing to a want of proper cleanliness, eating with unwashed hands; sometimes by the lungs, as in the case of smelters and white lead makers who are exposed to the fumes; and occasionally by absorption from mucous surfaces and perhaps the skin.

Previous ill-health, excesses of all kind, insufficient food, and insanitary houses are powerful predisposing causes of toxic symptoms among lead workers.

Symptoms.—The toxic effects of lead sometimes run an extremely acute and rapid course, either in those exposed to the poison for the first time, or after a long period of exposure and possibly the manifestation of the more chronic symptoms. Most of the acute cases are to be found among those who have been submitted to the vapours of lead, and, as Dr. Oliver has shown, are much more frequently young females; indeed, contrary to what has been generally held, he attributes a special predisposition to the feminine sex, and finds in the prominent symptoms, such as the anæmia, a support for this view.

The acute symptoms, which may come on suddenly, are frequently those resembling hysteria, with anæsthesia, dimness of vision, and headache. With removal from the cause and appropriate treatment, the patient may exhibit no other symptoms, unless they be those of a mere chronic intoxication, such as a blue line on the

gums, anæmia, etc., to be presently described. Or convulsions of an epileptiform character may supervene and continue with loss of consciousness, to be succeeded by violent delirium or a melancholic stupor, and end in the course of a few days in a fatal coma. Only a small proportion of cases which exhibit these serious symptoms recover, and then frequently with some permanent impairment of sight or memory.

As a rule, however, lead poisoning is insidious in onset and of very slow progress. The key to the trouble seems to be the fact that lead is a protoplasmic poison, with perhaps a special preference for certain glandular tissues and plain muscular fibres. The food is improperly digested and imperfectly absorbed; the blood is defective in quality; the tissues tend rapidly to degenerate, and glandular tissues of great functional importance tend to be replaced and encroached upon by connective tissues, or, in other words, there is a tendency to fibrosis of various organs—kidneys, liver, nerve centres, nerves, and arteries—with degeneration and atrophy of their protoplasmic elements. The kidneys are especially liable to become fibrotic, and thus an important channel of elimination is to a great extent blocked and the vulnerability of the individual to his noxious surroundings is immeasurably increased. Indeed it is to the structural and consequent functional damage inflicted on these excretory organs that Dr. Oliver attributes the severe cerebral symptoms met with, ascribing them to auto-genetic toxins. Previous to and accompanying the special symptoms there are usually observed anæmia, loss of appetite, a metallic taste and sickness, the last being of very variable occurrence.

The *anæmia* is most characteristic, and dependent on it are the various evidences of impaired nutrition due to an impoverished blood. It is said that iron is mainly eliminated by the skin in acute plumbism, thus causing the profound anæmia.

The most common ailment of the lead worker is *colic* of a paroxysmal or almost continuous character, due to a tonic contraction of the intestines, which may last for some time, producing great pain and perhaps tenderness, and generally absolute constipation. The abdomen is, as a rule, hollow and the muscles rigid; the pulse, which is small and hard, is not increased in rapidity, and the temperature is not raised. This symptom of lead intoxication occurs whatever the channel by which the poison is introduced into the system. Whilst the colic persists the urinary secretion is much diminished.

A sign of great value, which serves to guide the practitioner in his diagnosis, is a *blue-black line upon the gums* close to their margins.

This is very often present in lead workers, and is due to the deposition of lead sulphide within the tissue of the gum itself. The precipitation of the lead in the blood-vessels or tissues of the gum is brought about by the action of the sulphuretted hydrogen formed by the decomposition of albuminous food particles in the mouth. The lead line, *cæteris paribus*, is best marked in those with dirty mouths and ill-kept teeth. If the mouth be kept clean and the teeth be carefully brushed there may be no "lead line," notwithstanding that the patient is undoubtedly suffering from chronic lead poisoning. The "lead line" is absent in places where teeth have been removed, but occasionally dark stainings of the buccal mucous membrane are observed in cases of lead poisoning.

Painters and plumbers are often great sufferers from *gout*, a fact which is presumably dependent on the sclerosed condition of the kidneys interfering with the due elimination of uric acid. Sir Alfred Garrod showed that in a person of a gouty tendency an acute attack could be determined by the administration of a few grains of lead acetate. For some cause or another the lead worker appears to be far more liable to suffer from gout in London and the south of England than in Newcastle and the north of England and Scotland. The reason for this is not quite clear. Pains in the joints are common in lead workers as they are in all gouty subjects, but it would be rash to conclude that these "arthropathies" are all due to the deposit of urate of soda. Some are possibly "neuropathies" and dependent on those chronic changes in the nervous system from which lead workers are liable to suffer. Also owing to the renal changes *albuminuria* is a tolerably constant symptom, both in the acute and chronic forms of lead poisoning.

Definite and characteristic *nervous affections* are common in the lead worker. The most common form is "*wrist drop*," due to a paralysis of the extensors of the wrist and thumb. It is generally symmetrical, but in right-handed persons is usually more marked on the right side. This is probably due to a neuritis of the posterior interosseous nerve, and not infrequently there is marked tenderness of the trunk as it passes round the head of the radius. This paralysis might be accounted for by a symmetrical lesion of the anterior cornua and motor cells of the spinal cord, but apart from the nerve tenderness, the power of rapid recovery in cases of wrist drop makes this explanation improbable. There are no sensory disturbances, and the muscles give the electrical reactions of degeneration and waste rapidly. As a rule the loss of power precedes the wasting, but sometimes both imperfections progress

together. Any case of paralysis of the extensors of the wrist and hand without implication of the supinator longus is probably a case of lead paralysis. The way in which the supinator longus stands out from the wasted arm is characteristic, and if the patient, with his elbow at a right angle and the hand held by the physician midway between pronation and supination, be asked to further flex his elbow the supinator longus may be seen to contract vigorously. This serves to distinguish lead paralysis from that due to pressure upon the musculo-spiral nerve, which is occasionally seen in a drunkard who has unduly compressed the nerve between his heavy head and his humerus, by using his arm as a pillow during a drunken slumber on the ground. In this form of musculo-spiral paralysis there is generally "numbness" of the back of the hand, and the affected muscles usually respond to faradism, as pointed out by Duchenne. Sometimes the small muscles of the hand are affected as well as the extensors of the wrist and fingers, and rarely may even suffer first, simulating in some measure the commencement of progressive muscular atrophy, which may be distinguished by the wasting of the muscles preceding the paresis and by the presence of fibrillary twitchings.

Although "wrist drop" is the typical form of lead paralysis, it must be remembered that paralysis due to lead is really protean in form, and in all cases, especially of "peripheral" paralysis, lead as a possible cause has to be considered. A few years ago one of the writers had a patient under his care at University College Hospital, who, in addition to typical wrist drop, had a paretic condition of almost every muscle of the body, including the adductors of the vocal cords.

Among the other nervous symptoms met with among lead workers *headache* is perhaps the commonest, but muscular pains and tremor, inequality of the pupils, optic neuritis, perverted or diminished cutaneous sensibility, and increased knee-jerks are among others that are met with, and very occasionally cases resembling general paralysis and others with marked ataxic symptoms have been described.

Menstrual disturbances are frequent, and pregnant women tend to miscarry.

Prognosis.—This chiefly depends in the chronic cases upon the duration and severity of the symptoms. Under appropriate treatment the colic, and even fairly marked cases of peripheral paralysis, will recover, and so long as exposure is avoided will not recur. But if the paralysis be of long standing and associated with

evidence of renal disease and profound malnutrition, only moderate improvement is to be looked for. It is not to be denied that the symptoms of plumbism, although apparently cured, yet signify an underlying impairment of health and susceptibility to disease which are liable to assert themselves, and especially by the pursuance of unhealthy modes of living, foremost among these being alcoholic excess.

Post-mortem appearances.—Besides the fibrotic changes in the organs already referred to, the kidneys in the acute cases exhibit a condition of tubal nephritis. The brain is pale and firm, or œdematous. Lead may be extracted from many of the tissues, especially the liver and brain.

In the **treatment** of chronic metallic poisoning the first essential is to remove the cause, or to take the patient away from his dangerous surroundings. All articles of food, drink, and luxury, such as snuff, tobacco, hair-dyes, and clothing have to be scrutinised with a view to detecting the source of the trouble, and it must be remembered that no quantity of any lead salt, if taken continuously, is too small to be dangerous.

The thorough ventilation of the workshop is probably the best protection for the artisan, and to this must be added the choice of wet methods of manufacture in preference to those which produce a fine and highly dangerous dust. The lead worker must pay the greatest attention to his personal health and cleanliness. Overalls should always be worn when at work, and every part of the body, including the head and hair, should be washed every day. Especially great care must be taken to wash the hands before meals, and to use a tooth brush night and morning. The worker must be properly fed, and must, if he is to avoid the dangers of his occupation, be strictly temperate. As abstention is easier than abstemiousness, it is probably wise for a lead worker to abstain entirely from alcoholic drinks, and so lessen the risks of acquiring a granular kidney and a tendency to gout.

The treatment of lead poisoning by drugs is of doubtful utility. It has been recommended to provide a "lemonade" as a drink for the work people, made with sulphuric acid instead of lemons. This is with a view to converting the lead in the alimentary tract into a comparatively insoluble lead sulphate. But lead sulphate is, if not soluble in water, easily digestible in the alimentary tract, and the work people cannot be induced to take this "lemonade" for long, for not only has oil of vitriol, even when diluted and sweetened, few attractions for the human palate, but is apt, of itself, to produce stomach-ache and constipation.

The chief channel for the elimination of lead appears to be the liver, which excretes the poison in the bile and so into the intestine, and it is essential in all cases of lead poisoning to keep the bowels freely open. The kidney appears to take but small share in the removal of the metal.

Potassium iodide is generally given with a view to assisting the elimination of the lead, and the opinion of most physicians is that patients improve while taking it, but the degree to which the output of lead from the system is increased during its exhibition is doubtful. Sodium chloride has been by some considered as more efficacious in this respect.

Warm bathing, and especially warm sulphur baths, have always enjoyed a deserved reputation for the cure of patients suffering from the paralytic and articular troubles which are caused by lead. The warm baths of Bath used to be much patronised by those who suffered from "the endemial colic" of Devonshire in the days before Sir George Baker pointed out that this *Morbus Colicus Damnoniorum* was really caused by the leaden clamps of the old Devonshire Cyder Press. The remedy is no less valuable now that lead colic is properly understood. The intestinal pain may require opium for its relief, and this is best given as the tinct. chloroform et morphinæ (B.P.), combined with full doses of sulphate of magnesia, twice or even three times daily.

Massage of the paralysed muscles and the passive movement of joints, combined with a maximum of fresh air, are of undoubted use. The employment of electricity for the stimulation of the atrophied muscles is also of great service, but I am inclined to advise that neither rubbing nor electricity should be used so long as the nerve trunks are tender. The application of blisters over them is a measure which hardly ever fails to give relief.

NOXIOUS GASES

Contamination of the air respired may be due either to an excessive amount of those impurities which the process of respiration communicates to it, or to the accidental admixture with deleterious gases derived from factories, mines, sewers, fires, illuminant gases, etc. Imperfect ventilation determines the presence of carbonic acid beyond that which may be regarded as the limits of health, viz. .02 per cent, and equally to the same cause is to be attributed the deficiency of oxygen and the presence of volatile emanations from the surface of the body and perhaps from the lungs, although it has

been recently denied on experimental grounds that any such poisons are given off by respiration.

The effect of breathing such air, as in crowded meetings, ill-ventilated apartments, etc., is usually to produce headache, drowsiness, a sense of lassitude and a quickened respiration of increased depth. But individuals, however, vary very much in their susceptibility to the effects of a "stuffy" atmosphere, the above symptoms invariably following in some, whilst others are quite unaffected. A constant exposure to such a condition tends to deteriorate the general health and leads to anæmia, loss of appetite, and muscular and mental enfeeblement.

Among the most important of the accidental gaseous constituents of the atmosphere are—

CARBONIC OXIDE.—This occurs from an escape of coal gas, the fumes of kilns, charcoal and coke fires, or from "after-damp" in mines. The prejudicial effect of the gas is due to its forming with the hæmoglobin of the blood a more stable combination than oxygen does, the latter becoming displaced and symptoms of oxygen starvation ensuing such as takes place at high altitudes (see vol. i. pp. 19-20). It has been ascertained by Haldane (*Jl. Physiol.* 1895) that symptoms are not apparent until the corpuscles are about one-third saturated, and that at half saturation they become urgent.

SEWER GAS.—The nature and composition of sewer gas, as well as its effects upon the human organism when respired, vary very greatly with the efficiency of ventilation of the drains and the completeness with which they are flushed and their contents discharged. When these conditions are satisfactory the air of the sewers has been shown to be much better than is generally supposed, and superior to what often obtains in public buildings and even private houses, the CO_2 being about twice and the organic matter three times as great as in the outside air at the same time. Even in respect to micro-organisms the number was found to be less in the sewer air as compared to the external atmosphere at the same time; and moreover, as shown by Mr. Parry Laws in his report to the London County Council, 1893, those micro-organisms that are met with are related to those of the outside air and not to those of the sewage, and are chiefly moulds and micrococci. These comparatively harmless characters of the air of properly ventilated sewers are borne out by the generally healthy condition of those individuals who work in the sewers and are continuously inhaling the air therein; nor is it a question of acclimatisation on their part, since no ill effects happen to the unaccustomed. When, however, the

drains are imperfectly ventilated and insufficiently flushed, so that the contained gases are confined and the sewage stagnates, the emanations therefrom may be very distinctly and even virulently toxic in character.

The **symptoms** of the more severe type are mainly those of gastro-intestinal irritation, vomiting, purging with headache and prostration, and even rigors and high temperature, albuminuria and petechiæ have been noticed. More commonly the effects are due to the constant breathing of an atmosphere only mildly impregnated with the sewer gases, such as may escape from a leaking drain into a sleeping apartment. In such cases the symptoms are less acute in character, and a vague sense of illness, with generally impaired health, headache, nausea and frequent sickness, with irregular pyrexia, are the chief features noticed, varying much in their relative predominance. Much difference of opinion has existed, in the absence of precise data, as to the responsibility of sewer gas for the production of specific infective diseases. A special form of sore throat, marked by an intensely angry and livid appearance of the fauces and extreme sense of illness, though only slight pyrexia, has been described as peculiar to the breathing of drain emanations. Cases of enteric fever, and perhaps cholera, have apparently been traced to a similar cause, and have been explained by the bursting of bubbles of gas from typhoid contaminated sewage, liberating the specific bacilli into the atmosphere, which thus obtain entrance to the body. Without denying the possibility of this, it would seem to be more probable to ascribe the incidence of typhoid fever in individuals exposed to sewer gas and without other obvious mode of infection to the deteriorated health caused thereby and the consequent greater vulnerability to the specific organism. It has also been suggested that exposure to sewer gases might increase the virulence of microbes of slight toxic power, which, but for this circumstance, might be harmless. Some experiments conducted by Mr. Shattock with the bacilli of diphtheria gave no support to this view (*Tr. Path. Soc. Lond.* 1897-98).

These various ill effects, which are of undoubted occurrence, although marked differences in the susceptibility of individuals are observable, are to be attributed in part to the constituent gases of the emanations, chief of which are carbonic acid, sulphuretted hydrogen, sulphide of ammonium, carburetted hydrogen and complex ammonia compounds, in addition to which volatile ptomaines and leucomaines have been regarded as being present. Dr. Klein (*Lancet*, July 8, 1899) has described pathogenetic microbes peculiar

to sewage, but whether these are liberated into the gaseous emanations therefrom is unknown ; though the observations of Mr. Laws already referred to would seem to negative such a conclusion in well-arranged drains. (*See also report to the London County Council on the bacteriological examination of sewage by Dr. F. Clowes, 1898.*)

Removal of the cause or of the patient from the locality is obviously the first indication for **treatment** ; in addition stimulants and oxygen inhalations are called for in serious cases.

SERPENTS' VENOM

The secretions of the parotid glands of certain vipers (*e.g.* the adders and rattle snake) and colubers (*e.g.* cobra, moccasin, and coral snakes), when introduced into the tissues of man and animals, are capable of inducing serious and frequently fatal results. The active toxic agents are proteoses, which Dr. S. Martin regards as being formed by the hydrolysing action of the epithelial cells of the poison glands on the albumens supplied to them from the blood. In this respect they are to be compared to the proteoses formed by the *B. diphtheriæ*, with which also they appear to closely correspond in degree of virulence. The process of hydration of the albumens in these cases does not proceed beyond the formation of proteoses (proto- and hetero-) to the production of peptones, such as follows on the action of pepsin or trypsin or even of the *B. anthracis*.

Symptoms.—These vary with the mode of introduction and quantity of the poison, the idiosyncrasy of the individual, the condition of the reptile, and still more upon the species of snake from which the venom is derived.

Experimentally it has been found that the poison obtained from the viperine forms exercises an exceedingly destructive effect upon the blood corpuscles, causing them to break up and discharge the hæmoglobin, which however remains unchanged ; the activity of the leucocytes is diminished ; the coagulability of the blood is increased, though if the dose of venom be very small this condition is quickly followed by a "negative phase" (Wooldridge), in which the blood either fails to clot or only does so after a long interval, and hence the marked fluidity of the blood after death ; and the germicidal action of the serum is deteriorated. A change is also induced in the walls of the capillaries whereby they readily permit exudation of the contained blood. The heart power markedly and rapidly fails and the blood pressure falls. Cobra poison on the contrary produces very little effect upon the blood or vessels, and much less effect on

the heart. The general action of all these venoms on the nerve centres is to diminish the reflex activity of the spinal cord, the cobra poison predominantly affecting the respiratory centres as well as the muscle nerve endings. Both elevation and fall of temperature have been observed.

Clinically corresponding with these experimental results are marked differences in the symptoms exhibited by man when bitten by one or other of these two groups of serpents. In both cases the site of the wound quickly becomes painful and swollen, to be followed by symptoms of weakness and prostration, arising more rapidly and more intensely on the bite of a viperine species and accompanied by further signs of blood change, such as œdema and discoloration of the limb, spreading, if the patient survive the first few hours, to the trunk and face, with petechiæ or considerable sanguineous extravasations. Later suppuration or gangrene of the region of the bite may occur and lead to death long after. If, however, a fatal termination occur earlier the prostration deepens and all the symptoms of rapid cardiac failure are manifested, sometimes with delirium. Paralytic symptoms are more characteristic of the cobra bite, affecting the tongue and larynx as well as the limbs, and gradually extending to the muscles of respiration, the pupil remaining contracted almost to the end. There is often no marked loss of consciousness, though the patient appears more or less drowsy. A further notable difference between these groups of toxins is seen in their effect upon the kidney, by which it is proved they are (possibly with the salivary glands) eliminated, for whilst the viperine poison causes albuminuria or even hæmaturia, this is not the case with the cobra poison.

In all cases where recovery takes place it commonly does so remarkably quickly, the patient becoming himself within a few hours. Death usually takes place in from six to twelve hours, though occasionally in a much shorter time, and sometimes not for two or three days.

The **post-mortem** appearances differ in the two forms, especially as regards hæmorrhagic extravasations, which are abundant and widely distributed in death from viperine poison, and but slightly marked in the other, the kidneys in the former case also presenting a condition of acute degeneration.

Treatment.—If time permit, every effort should be made to prevent the absorption of the poison from the wound by ligaturing the limb above the site, freely incising, sucking, and washing with Condyl's fluid, cauterisation or even amputation. Injections of calcium

hypochlorite, or of gold chloride, into and around the seat of the wound have been specially recommended by Dr. Calmette. Stimulation by alcohol, subcutaneous injections of strychnine, or intravenous injections of liq. ammoniæ are called for, not as antidotes to the poison, but to sustain the patient if possible long enough to permit the effect of the venom to wear off, as it frequently does, most unexpected recoveries sometimes occurring. To the same end artificial respiration should be perseveringly resorted to. Considerable success has followed from the labours of, among others, Dr. Calmette and Professor Fraser in preparing an antivenene by the continued inoculation of animals (horses) with an attenuated venom. The immunity conferred by this agent appears to be of short duration, but its antidotal power seems to be undoubted, cases apparently moribund having recovered after its use. The dose recommended to protect from a lethal dose of venom is from 10 to 20 cm., but this might be doubled in very severe cases. But this procedure should not replace the treatment of the wound and general stimulation already described.

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W. H. ALLCHIN.

PRIMARY PERVERSIONS OF GENERAL NUTRITION

The term "nutrition" may be taken to signify the chain of processes upon which depends the maintenance of the life of the individual. These processes necessarily consist of those whereby the ingesta (food and air) are prepared and brought into suitable relation with the blood and lymph currents, into which they are absorbed (digestion and inspiration); the subsequent stages of elaboration which are assumed to take place during absorption and in the circulating fluids; the still more complex changes of a constructive (anabolic) character, only dimly conceived of as occurring within, or within the range of influence of, the living matter itself; and lastly, those destructive or catabolic changes, the final results of the metabolism being ultimately excreted as more or less known, and stable substances by the lungs, skin, kidneys, and intestinal tract. With this interchange of material effected by the bioplasm is associated a conversion of the potential energy possessed by the material into kinetic energy of certain specific kinds, such as muscular, nervous, glandular, together with heat and electrical manifestations, which together make up the life or nutrition of the individual.

Defects in the quality or quantity of the ingesta, in the functions of digestion, inspiration, or absorption, or in the metabolic processes (constructive and destructive), or failures in excretion, are the causes of *malnutrition*, which thus may be primarily due to external conditions such as deficient or improper food, or vitiated air, or to mal-assimilative power on the part of the living cells, whether hereditary or acquired, or to imperfect excretory capability on the part of the organs concerned. It is not conceivable, however, that in the complex organism, any one of these defects, dietetic, metabolic, or excretory, is alone responsible for the symptom-group which characterises any form of malnutrition. Errors in diet must lead to an impairment of the structure and functional capability of the bioplasm, just as initial defects in the living matter itself will determine functional perversion, or as mal-excretion with retention of waste products may lead to imperfect performance of any or all of the nutritive processes.

For the due performance of the processes of nutrition, two different influences, originating within the organism itself, would seem to be necessary. Of their real nature but little is known, and indeed their existence is in the main a matter of hypothesis based less upon the study of healthy vitality than of certain manifestations of disease.

Neurotrophic influence.—It is assumed that among the various impulses which emanate from the nervous centres, cerebrospinal and ganglionic, some are concerned with directly controlling the nutritive

activity of the various tissues, comparable to those which regulate the secretory processes of glands. The ground for the assumption of these trophic stimuli is chiefly to be found in the very obvious tissue changes, such as wasting of muscles and bones, disorganisation of joints, and atrophy of skin and its appendages which follow the division of nerves supplying these structures, or the destruction of certain tracts of nerve cells with which these nerves are connected. Following upon this idea of the normal nerve-governance of nutrition is that of trophic disturbances resulting from irritation of the "nutritive centres" resulting in tissue changes of various kinds, atrophic, hypertrophic, degenerative, etc., together with such perversions of nutrition as are represented by rheumatoid arthritis, diabetes, or obesity, all of which are regarded by some as forms of tropho-neuroses.

Internal secretions.—Whilst we may suppose the nervous influence on nutrition is of the nature of a stimulus exerted on the bioplasm, both in its anabolic and its catabolic activities, in virtue of the ultimate structural continuity between the nerve and tissue elements, the other modifying influence on metabolism is of a more material character, viz. the "internal secretions" of the ductless glands, of glands that furnish "external secretions," and probably also of other organs with which glandular functions, as ordinarily understood, are not usually associated. Among the factors of the tissue environment other than the food supply and the trophic nerve governance, there is good reason to postulate a nutritive influence mutually exerted through the agency of substances derived from the biochemical changes of tissue metabolism which are thrown into the blood or lymph channels. Such a conception would give a wider extension to the range of internal secretions. The very grave disorders of general nutrition which follow on experimental removal or destructive disease of certain ductless glands show without doubt that the integrity of these structures is essential to the general well-being, and that their influence is exerted by means of some material formed by them and thrown directly into the blood-stream, or indirectly by the lymphatic channels. The precise mode in which these internal secretions act upon the tissues and effect their metabolism is quite unknown, and except for the colloid material of the thyroid body, no actual secreted substance has yet been isolated.

This view of the nature of nutrition and of the conditions upon which it and malnutrition depend, attributes but little share in the result to the quality and character of the material—bioplasm—through which the phenomena are manifested. Formerly, much importance was attached to assumed defects in the intimate composition and molecular constitution of the living matter, such imperfections being regarded as the material basis of morbid constitutional states or "diatheses," such as the gouty, the scrofulous or strumous, the rheumatic, the arthritic, etc. An underlying tendency to disease in one or another direction was

supposed to exist, which might be sufficiently potent to become manifest irrespective of surrounding conditions, or might require some external stimulus to cause it to develop. So also it was customary to recognise certain healthy constitutional states or "temperaments" associated with more or less well-marked structural peculiarities, of the integuments and appendages, of the bones and contour of the face, the general physique, etc., which were further supposed to predispose to certain phases of ill-health. At the present day, owing in great measure to the widely extended knowledge concerning causes of disease furnished by the environment, and especially the subject of microbic poisoning, far less importance is attributed to the inherent character of the living material, which it is possible there is now an inclination to overlook, especially since its nature is so largely hypothetical, and has not been brought to the test of exact observation. Consistent with the admittedly large part that external conditions have in the production of disease, it is now customary to express the share taken by the living matter by such terms as that it is "less resistant" or "more vulnerable," and though no explanation is offered of the immediate cause of such a state, which fundamentally must depend on some structural—molecular—perversion, it is, nevertheless, to such a conception that we are inclined to refer the explanation of the hereditary element in disease, so far as that is admitted to have any reality. And as the number of those maladies which were formerly regarded as being hereditarily transmissible is now much curtailed, so those diseases which were spoken of as "idiopathic" are similarly fewer. That the living matter does vary in the perfection and quality of its inherent potentialities may be taken for granted since no two individuals placed under exactly similar conditions are identically alike, and consistent with our fundamental conceptions of the cosmos, these differences must be associated with and perhaps depend on ultimate structural—molecular—differences. If, as seems convenient, the constitution of the individual be regarded as the sum of the tendencies possessed by its component living units, it is clear that some of these tendencies are hereditarily derived as others may be acquired. In obedience to the former, the fertilised germ develops into the likeness of its ancestors, but how far this likeness may extend to repeat defects of the parent organism, to the transmission of characteristics which may have been acquired as morbid states, remains an unsettled biological problem.

In a wide sense, malnutrition may be regarded as synonymous with disease, the various forms of which being considered as so many forms of impaired nutrition. No doubt, a diseased state, however local it may appear to be, nevertheless does produce effects on the general bodily well-being, and by so much interfere with the normal performance of processes upon which the mere existence of the individual depends; and obviously it is not sought to maintain that the introduction of

poisons, microbic or other into the body, does not profoundly modify the general nutrition. But the clinical course of such cases, more especially if they be acute in character, differs so widely from those more lasting general states of ill-health in which the organ or tissue primarily involved is sometimes as doubtful as the actual cause, as to warrant, if only for convenience sake, a different nomenclature; and in this it is that such a group of diseases as is now to be considered, finds its provisional justification both in separation and in name. And further, it may be observed that those maladies included within the foregoing groups, such as syphilis, alcoholism, or plumbism, which exhibit a chronic course, closely approach in their clinical characters and effects to those about to be described, some of which would seem to be largely conditioned by, though not entirely due to, imperfections in the ingesta or other external circumstances. Consistently, however, with prevailing biological conceptions, it is to the intrinsic character of the living substance itself that these maladies are rather to be ascribed. Defects in its quality and nature, whether of hereditary origin or inflicted upon it as the result of former disease—apparently recovered from—or long continued untoward conditions, render it less resistant and more easily susceptible to those injurious influences, from wherever derived, which in its normal integrity it might have withstood. In the complex interactions between the living matter and its environment, made manifest either in health or disease, it is impossible to apportion to each its exact share in the result, but regarding each in its way and to an unknown degree as responsible for the outcome, it is rather to primary imperfections of the living tissues that we are inclined to attribute the development of these maladies, fully admitting the need there may frequently be for external influences to call this predisposition into activity.

Suggestive also of a common origin of these diseases in the fundamental metabolic processes of the tissues is the frequency with which two or more may co-exist in the same individual, or the occurrence among different members of the same family of one or other of this group of maladies; gout, obesity, diabetes serve to illustrate this statement. It may be further remarked that many of these, so to say, correlated diseases, afford the best examples of inherited maladies.

Whilst so much uncertainty exists as to the intimate nature and causation of many of these states of ill-health, any attempt at classifying them can only be imperfect and unsatisfactory, and no claim for scientific precision is made for the arrangement here followed.

A fairly well-defined group of morbid states, for the most part acute in course and to be compared with the effects of the poisons just treated of, are those due to toxic materials developed in the body itself in the course of some perversion of tissue metabolism—the AUTOGENETIC POISONS.

Another, and almost natural group, are those structural defects of a

degenerative character, some of which, as senility, are developed in the course of a normal existence, though in excess, or when premature, they may give rise to very definite disease. Such are collectively known as **RETROGRESSIVE CHANGES**. These are for the most part of widespread occurrence, scarcely any organ or tissue being exempt, and hence some general account of them is requisite, preliminary to the descriptions peculiar to the several organs involved, under which they will be more specifically considered.

In contrast with these are **PROGRESSIVE CHANGES** represented by **HYPERTROPHY**. And closely connected is the subject of **INFLAMMATION**, which deals with those complex tissue changes and symptoms which follow the application of an irritant.

The importance and frequency of the symptoms connected with the development of **MALIGNANT GROWTHS**, render desirable some general remarks on the nature and origin of these typical perversions of nutrition.

DISEASES OF CERTAIN OF THE DUCTLESS GLANDS, with consequent alteration in their internal secretions, underlie such maladies as cretinism and myxœdema, exophthalmic goitre and Addison's disease.

And lastly is that heterogeneous group of clinical entities, comprising obesity, diabetes insipidus and mellitus, gout, rheumatoid arthritis, chronic rheumatism, myalgia, rickets, acromegaly, osteitis deformans, and mollities ossium. No satisfactory classification of these can be made at present; the uncertainty as to their intimate pathology and causation forbid the attempt. Whilst all represent in a greater or less degree metabolic imperfection, many appear to depend on some ill-directed nervous influence, as some seem to owe their existence to defects in the waste excretion or perhaps to alteration in an internal secretion, and others may ultimately find their proper place among the infections.

Those maladies which may reasonably be regarded as **TROPHO-NEUROSES** will be described with other diseases of the nervous system.

W. H. ALLCHIN.

AUTOGENETIC POISONS

The organism, apart from its exposure to noxious influences which may affect it *viâ* the alimentary canal, the lungs, or the skin, is also liable to be poisoned by substances which are formed within the body itself, either (α) in the course of the digestive and other processes which take place in the contents of the gastro-intestinal tract, and will be more conveniently treated of with disorders of digestion ; or (β) in the complex metabolic changes associated with tissue nutrition. Although thus distinguished by their origin, it is undesirable, and probably incorrect, to suggest any essential difference between them in their nature or in their effects, or indeed to separate them from poisons of extrinsic source, such as the microbic toxins, snake venom, ptomaines, and alkaloids. All are inimical to healthy bioplasmic activity and as such are poisons, and frequently similar in their effects ; the exigencies of arrangement are the sole ground for their separate grouping.

Our want of precise knowledge concerning the chemistry of nutrition, of the exact composition and molecular constitution of the complex bodies which intervene between the ingested food-stuffs and the eliminated waste products, prevents anything approaching accuracy in definition of the toxic substances the effects of which we clinically recognise. Associated more or less constantly with certain forms of renal disease and alterations in the composition of the urine are symptoms which are conventionally termed *uræmia* ; in the course of some cases marked by jaundice, symptoms arise which are spoken of as *cholæmia* ; and many diabetic patients develop clinical features such as coma, which have been referred to as *acetonæmia*. These names are merely temporary makeshifts, not one is strictly correct in its denotation, and it is probable that the conditions are not as distinct from one another as their associations might imply, and that the essential poisons in each case are very similar, if not identical. The same might be said for that symptom-complex known as "the typhoid state," a most convenient phrase that signifies a well-defined group of phenomena occurring in the course of so many fatal diseases. Besides these several states there are without doubt others which have not hitherto received distinctive names that accompany the termination of malignant disease, and other chronic wasting maladies, and indeed that are present in some degree in all lingering deaths. It will be found that there is a considerable resemblance in the symptoms manifested in these various conditions, and further that they are chiefly characterised by disturbed cerebral activity.

The difficulty in a complete understanding of the subject of auto-

intoxication, as indeed in the poisoning of external origin, is that resulting effects are in all probability due not only to the direct effect of the poison upon this or that organ, but also to the secondary nutritive disturbances induced by the perverted action of the structures primarily involved. It is almost hopeless to attempt to differentiate these, but the complex nature of the symptoms presented should not be forgotten in their investigation or attempted treatment. The functional disturbances set up would seem most probably so to react on each other as to lead to a condition which the organism cannot withstand, or that in other cases may conceivably neutralise each other to the benefit of the patient.

Of the intimate nature of these self-developed poisons nothing positive can be affirmed. Some are probably albumoses or kindred substances, others no doubt resemble the vegetable alkaloids in composition. A further difficulty in connection with this subject is the doubt as to how far the mere retention in the blood of waste materials, which are normally produced and excreted, is responsible for the toxic effects, or whether these are wholly or only in part due to the formation of abnormal bodies produced in the course of the disturbed metabolism; nor does the analysis of the excreta settle the point, inasmuch as it is still uncertain what changes are normally effected in the waste products during the course of their elimination by the excretory organs. Whilst yet another difficulty exists in our almost complete ignorance of the nature of the excretion that takes place by the alimentary canal, and the conditions governing the absorption of toxic bodies therefrom.

URÆMIA

SYN.: RENAL TOXÆMIA

Symptoms.—The symptom-group to which this term is applied consists of manifestations which in the main are nervous in origin and character. Sometimes of sudden onset and rapid course, at others developing insidiously and of long duration, they are described as acute and chronic, and in the former case may be the first and only evidence of an unsuspected illness that is fatal within a few days. The several symptoms to be described vary in their relative frequency of occurrence and predominance, some being fairly constant, others of more exceptional appearance; but inasmuch as the state known as uræmia almost invariably occurs in association with some obvious structural change in the kidneys, there are super-added the various symptoms of renal disease, between which and uræmia it is not always possible to draw the line. Among the most prominent of these associated signs are anasarca, cardio-

vascular phenomena, retinitis, albuminuria, hæmaturia, and various rashes.

ACUTE URÆMIA.—This condition may develop in the course of an acute nephritis, when the kidneys have been previously healthy, or may supervene during the progress of chronic renal disease. In a patient known to be the subject of renal disease, or perhaps in one who has not previously exhibited symptoms of illness, there may suddenly supervene a state of drowsiness that rapidly deepens into stupor and coma. Not infrequently this condition may have been immediately determined by some unusual fatigue, an accident, or even a surgical operation, by a drinking bout, or by some acute illness such as pneumonia, endocarditis, or erysipelas; a very rapid absorption of an extensive anasarca has been supposed to precipitate an attack of uræmia. The coma closely resembles that caused by cerebral hæmorrhage or by narcotic poisoning, although it is usually less profound and the patient is capable of some degree of rousing.

Or the first manifestation of the toxæmia may be an attack of epileptiform convulsions, preceded, it may be, by some slight muscular twitchings, or by transient rigidity or by severe cramps especially in the calves of the legs. As a rule the convulsions are general, commencing in the smaller muscles of the hand or face, but they are often unilateral, or one side is more affected than the other. The attacks may be repeated—even twenty times or more—the patient remaining unconscious in the intervals.

Among the other symptoms associated with the coma and convulsions, disturbances of respiration are the most constant. The rhythm of the movements may be interrupted and true Cheyne-Stokes' breathing may occur, or there may be paroxysmal attacks of an asthmatic character, which may be the most prominent symptom. The most characteristic and perhaps most frequent respiratory phenomenon is a regular, sometimes slow and deep breathing, not unlike that seen in apoplexy, except that in place of being stertorous it is of a peculiar hissing character. These several forms of dyspnoea are often most distressing to the patient, if conscious, though coma more often obliterates the suffering. The cardiac rhythm and pulse are also frequently altered, varying in some measure with the respiratory disturbance. And alterations in the size of the pupil may be also observed, more or less synchronous with the cardio-respiratory signs. Hiccough is sometimes severe and persistent.

The tongue is dry and brown, and the gums swollen and bleeding; the breath is offensive, and a distinctly urinous odour of the

body is generally perceptible. An attack of diarrhoea not infrequently ushers in the uræmia, and vomiting sometimes occurs.

The patient may become the subject of delusions; delirium, sometimes violent, is not uncommon, and may be among the first symptoms of the attack; mania and catalepsy have also been seen. Sensory affections, unless it be headache, are far less frequent, but temporary blindness and deafness have been complained of; the constant presence of some degree of stupor necessarily renders these symptoms less recognisable. A distressing wakefulness has been described as of occasional occurrence. Besides the various cerebral areas and centres which the poisons appear specially to affect as indicated by the manifestations described, those centres which control the heat production and loss are also very commonly involved. The body temperature in the uræmic state is generally subnormal, and may even remain so with such co-existing complications as pericarditis, pneumonia, or pleurisy; but pyrexia and hyperpyrexia may accompany the convulsive attacks, or even, it is said, the temperature may rise independently of these.

When the attack has complicated an acute nephritis the retinæ are unlikely to be affected, though a retinitis or hæmorrhage is almost invariable should the renal disease be of long standing.

The urine is generally diminished in amount and highly albuminous, but neither of these characters is invariably present.

The duration of what may be called acute uræmia varies from a few hours to a few days. Cases somewhat more protracted and marked by less severity of symptoms may be called subacute, but no marked characteristic serves to distinguish them.

The eclampsia of pregnancy and of labour, which closely resembles acute uræmia in its clinical features, and is almost constantly associated with albuminuria, doubtless owes its origin to a similar cause.

CHRONIC URÆMIA.—The close connection of this state with chronic nephritis makes a separation of symptoms impossible. It is only when there come to be superadded to the morbid states of the urine, of the pulse and heart, and of the retina and possible dropsy, certain symptoms of less constant appearance and betokening for the most part a fatal termination, that the specially toxic phenomena are considered to be present, but such a distinction is in no sense real or scientific. Some alteration of manner, with dragging speech and a foul tongue, may be the first indications. Many of those symptoms already enumerated as occurring in acute uræmia also mark the chronic condition. Headache, some-

times severe, is constant, though this is common in chronic renal disease apart from other toxic symptoms. Muscular twitchings are frequent, whilst attacks of interrupted breathing, particularly of the asthmatic type or of the Cheyne-Stokes' variety, and of hiccough are common; with these manifestations a variable degree of dulness, drowsiness, or stupor is also present, or there may be attacks of restlessness, the patient being kept quiet with difficulty. Vertigo or dizziness is sometimes complained of, as also is itching of the skin. As an exceptional occurrence paralysis, both monoplegic and hemiplegic, may be met with. The pupils are generally equal and contracted. Almost peculiar to the chronic stage, marked as it usually is by a subnormal temperature, are certain gastro-intestinal symptoms such as nausea, vomiting, and diarrhoea, which may be most distressing and intractable, and are most probably in great part nervous in origin, although the possibility of the last mentioned being due to intestinal ulceration should not be lost sight of.

Combinations of these symptoms in varying degrees of severity may last for one to several weeks, to be followed by almost complete relief, except from the more persistent manifestations of the causal renal disease; then after an uncertain interval to recur and again remit, and may thus continue over some months, whilst the general progress of the patient is usually downwards. But this is not always so, the first attack of these symptoms may proceed into a coma from which the patient never rallies.

For the **diagnosis** of this condition an examination of the urine, of the heart and pulse, and of the retinæ is imperative, and should not be omitted in any case of convulsions or coma, or of a combination of such symptoms as headache and vomiting, especially if any muscular twitching be superadded. Upon the information so obtained the recognition of uræmia may almost certainly be based. A general thickening of the arteries is seldom absent.

Post-mortem appearances.—These consist almost entirely of those changes in the kidneys, heart, and other structures which are associated with acute or chronic nephritis, and it is doubtful if any be absolutely distinctive of the uræmic state. The incidence of acute uræmia may be consequent on acute Bright's disease, when the kidney is enlarged, intensely hyperæmic, dripping with blood on section, and with an easily removed capsule, showing microscopically extensive desquamation of the epithelium which blocks the tubes with cells, granular débris, and blood, the change frequently affecting the Malpighian capsules especially; or in the course of chronic Bright's disease when the kidney is small, somewhat pale, with

thickened adherent capsule and granular surface, the "contracted white kidney." With the "large white kidney," in which the interstitial connective tissue is less involved and the capsule strips readily and leaves a smooth surface, uræmia of a chronic character appears to be more frequently associated, whilst the "red granular kidney" seems to be less often responsible for renal toxæmia, although it cannot be said that these distinctions are absolute.

Œdema of certain of the viscera is a fairly constant appearance, especially of the lungs and of the brain, even when there is no general anasarca. The "wet brain" of chronic alcoholism, so often the accompaniment of chronic Bright's disease, is of this nature, and represents what was formerly termed "serous apoplexy." The excess of fluid, however, may be more a consequence of cerebral atrophy than it is of active effusion.

Pathology.—The development of the symptoms described whether acutely or in a more lasting and repeated manner in the course of an existing disease of the kidneys, suggests as an explanation for their production, the failure in elimination of certain toxic substances, but although this may be in some measure true, it is not the whole truth; for it is found experimentally that by the removal of both kidneys in animals, or when complete suppression of urine is brought about by obstruction of the ureter, or by blocking of the blood-vessels of both kidneys, previously healthy (Dr. Bradford), in the human subject, that the symptoms which ensue differ markedly from those described, although the retention of waste and toxic bodies must be more complete than in most cases of nephritis. It is found that complete suppression may exist for several days with but very little disturbance of the patient, who remains quite sensible and free from convulsions, though the pupils have been noted as contracted and the temperature subnormal. After some days, perhaps as many as ten, slight twitchings are observed, there may be some nausea and vomiting; the patient usually dies from respiratory or cardiac failure, retaining consciousness. To this condition the name "latent uræmia" has been given, but it is altogether different clinically from uræmia as generally understood.

It would thus seem that mere retention of the urinary excretion will not wholly account for uræmia, unless indeed it be that latent uræmia depends on the retention of normal waste products which become toxic by accumulation, whilst uræmia proper is due to some abnormally produced bodies in the course of the perverted tissue metabolism connected with renal disease. For this view there are

some grounds. Dr. Bradford has shown experimentally that the kidneys exercise some special influence on the nutrition of the muscles, and that when as much as three-quarters of the normal kidney substance is removed the animal dies with the muscles loaded with nitrogenous waste. If by disease a similar amount of renal tissue is rendered incompetent, a like result may be supposed to occur, and support for this surmise is to be found in the undoubted fact that the blood and tissues generally in patients dying of uræmia are found to contain a very large excess of nitrogenous extractives, even where the secretion of urine and of urea has been fairly copious. It seems probable that the actual poisonous agents are to be found among these, though whether they are wholly abnormal substances formed under the abnormal conditions present, or whether they are the normal antecedents of urea is doubtful; probability points to the former hypothesis. Certain it is, however, that the deleterious agent is not urea as formerly supposed, and as the name suggests. Nevertheless urea is apt to be found in the excreta, vomit, sputum, and occasionally forms a deposit on the skin after the sweat has evaporated.

Whether the excess of cerebro-spinal fluid and œdema of the brain is to be held in any degree responsible for the symptoms designated uræmic must still remain uncertain. Alterations in the cerebral circulation, with or without œdema, have long been considered as the cause of the condition, rather than one of a toxic character, and recent observations have tended to attribute some share in the total result to vascular states. An increase in the blood-pressure, which is usually high in this condition, is liable to be followed by an acute attack of uræmia, due probably to the dilatation of the cerebral vessels (which Dr. L. Hill has shown is the accompaniment of general high tension) and consequent greater supply of toxic material to the brain. Moreover such measures as bleeding and purgation which lower the pressure are among the most effective means of relieving the symptoms or even averting their onset.

Prognosis.—The condition is always to be regarded even in its mildest form as extremely grave. The immediate forecast is difficult, since death occasionally follows on a single attack of convulsions, the individual never regaining consciousness, or temporary improvement and apparent recovery may succeed to a score or more of convulsive seizures spread over several days. Although an acute attack marked by considerable severity of symptoms may result in complete recovery when the underlying

kidney condition is acute, this is not to be expected when it occurs in the course of chronic nephritis. The general course of a chronic uræmia has already been indicated.

Treatment.—The importance of bleeding and purging and their rationale has been pointed out both as curative and preventive measures. A full dose of pulvis jalapæ co. or a few grains of calomel, notwithstanding the fact that mercury is generally contra-indicated in renal disease, are the most suitable aperients and should be given at the very first appearance of the characteristic symptoms. It may also be reasonably presumed that by these means toxic matters are removed by the bowel, since urea is found in the fæces.

Free sweating by the hot-air bath, or preferably by the subcutaneous injection of gr. $\frac{1}{3}$ of nitrate of pilocarpine, will frequently be beneficial, for undoubtedly it is desirable to obtain increased skin action, if only as a means of lowering the blood-pressure. Nevertheless improvement does not always follow, and repeated fits have been known to follow the hot-air bath. Most benefit is to be expected when the nephritis is acute.

For the relief of the convulsions and still more of the dyspnœa, morphia may be given in small doses (℥ v. to x. of the liq. morphinæ hydrochlor.), the effect being carefully watched. Inhalations of chloroform, amyl nitrite, nitro-glycerine, ammonia, ether, and similar remedies have been employed for the same purpose with varying success. Transfusion of neutral saline solution after venesection has also been recommended with the view of diluting the circulating poisons, and is found to be of especial value in the relief of convulsions.

The diet should be fluid, and principally milk or very thinly made Benger's food. It is desirable to avoid nitrogenous food and especially artificially prepared meat extracts.

CHOLÆMIA

SYN.: HEPATIC TOXÆMIA—TOXÆMIC JAUNDICE—ICTERUS GRAVIS

It is a matter of common experience that a very considerable degree of jaundice may be present, and even persist for days or even weeks, and yet be associated with few or no other symptoms, apart from digestive disturbances, certainly with none that can be regarded as toxic. There will probably be a slow and infrequent pulse, unless there be any pyrexia, and some itching of the skin may

be complained of, but not invariably, and there may be yellow vision ; but apart from these last-named symptoms the patient may be but little inconvenienced. From this it would appear that the circulation of a bile-containing blood is not of necessity a serious condition. But it is also well known that in many cases of jaundice, even almost from their first appearance, or it may be after the state has existed some time, there arise symptoms of a very grave and alarming character, which, from their similarity to those resulting from poison, are regarded as toxic in nature. To these the term "cholæmia" has been given, but since it is clear that it is not the bile which is the cause of the symptoms, the name can only be accepted provisionally and pending a more precise knowledge of the pathology of the condition.

The characteristic **symptoms** closely resemble those to be presently described as constituting the "typhoid state." There is the same prostration, apathy and stupor passing into coma, or a noisy semi-delirium, especially at night ; tremors, subsultus tendinum, and convulsions ; anorexia, dry brown tongue, and sordes on the teeth ; and pyrexia with quickened pulse, which becomes increasingly soft ; or the temperature, as in uræmia, may be persistently subnormal, with alternations of considerable elevation. Somewhat peculiar to the condition is a greater liability to hæmorrhage, as shown by epistaxis, hæmatemesis (black vomit), and petechiæ ; and there is undoubtedly a greater destruction of blood corpuscles than is met with in the other conditions comprised within the category under consideration. As compared with uræmia, there is far less liability to muscular twitching or convulsive attacks, and headache is not so constant. Many cases of hepatic cirrhosis exhibit in their final stages similar symptoms of toxæmic nature.

Pathology.—On examination of those diseases of the liver with which jaundice and these toxic symptoms are associated, such as poisoning by phosphorus, arsenic, or serpent venom, or certain acute infections, such as Weil's disease and yellow fever, or acute yellow atrophy of the liver and other forms of "malignant jaundice," it will be found that the obstruction to the bile flow into the intestine is not complete, and that there is more or less destructive change in the hepatic cells. The alterations in the character of the urine in these cases, whether it be a relatively large increase of urea, or an almost complete disappearance of this substance, together with the presence of abnormal proteid derivatives, such as leucin and tyrosin, would indicate that the toxæmia is fundamentally an expression of a profoundly altered nitrogenous meta-

bolism in which the urea-forming function of the liver is principally at fault. On such a view the connection of what is known as cholæmia with uræmia at least becomes probable.

ACETONÆMIA

Although the name "acetonæmia" has been given to that toxic condition which so frequently constitutes the final state of diabetes mellitus, it is certain that acetone is not the actual poison. What it is is uncertain, for though β oxy-butyric acid has been generally credited with being the specially noxious agent, recent investigations throw some doubt on this view. Whatever be the exact nature of the poison, however, it is one that is produced in the course of the tissue metabolism that constitutes the morbid process known as diabetes.

The symptoms of this condition, which are chiefly those of coma and a peculiar respiratory distress, are treated of in the description of diabetes mellitus (see p. 186).

THE TYPHOID STATE

The condition to which this term is applied is perhaps typically represented by a moderately severe case of typhus fever, but it is liable to develop in the course of many maladies which otherwise exhibit no clinical, etiological, or structural affinities. While especially liable to occur in the course of febrile affections, such as the specific infections, typhoid fever, variola, scarlet fever, erysipelas, septicæmia, or pneumonia, it may set in during Bright's disease, and thus constitute the essential phenomena of a uræmic attack.

The characteristic **symptoms** of the state are connected with almost every function of the body, though pre-eminently with the neuro-muscular system. No special phenomenon marks its actual onset, but it is noticed that the patient becomes more prostrate and feeble, lying on his back in an apathetic manner, tending to sink down into the bed and to move but little, scarcely if at all resenting such trivial discomforts as would otherwise call for a shift of position. The eyes are more or less closed, and, with some deafness, little or no notice is taken of what goes on around; the dulness and apathy deepens into stupor, from which he may at first be partly roused, but finally passes into coma, from which he may never rally. It requires some hours, or even several days for the fatal stage to be reached, and during that time the muscular prostration

increases, tremors or subsultus tendinum are noticed, and sometimes even general convulsions. The pulse is rapid, 120 to 150, extremely soft, and frequently dicrotic; the heart is correspondingly feeble in its action, and the first sound may be scarcely heard. The integuments may be flushed, especially in the later stages, when there is often profuse sweating. The breathing is shallow, and somewhat quickened, but often not in proportion to the pulse; but there is an extreme liability to hypostatic congestion of the bases of the lungs, and the character of the respiration will be largely conditioned by the degree to which this exists. The tongue is dry and later brown, the lips crack and sordes collect around the teeth, contributing to the offensive odour of the breath. The bowels may be either confined or loose, oftener perhaps the former, and the motions may be passed involuntarily. The urine is commonly scanty, high coloured, and of high specific gravity, containing a trace of albumen; retention is sometimes troublesome. According to the malady which the typhoid state has complicated will be the character of the temperature, but it is not to be forgotten that the condition may exist with a subnormal temperature, as in uræmic cases. Whilst the important features of the state are those of profound nervous or muscular prostration, "the precise grouping of the symptoms will vary in different cases, even of the same disease, while in diseases essentially different it may be identical" (Murchison on "The Typhoid State," *Brit. Med. Jl.* 4th January 1868).

The **pathology** of this condition is obscure. It is difficult to say that any one or more of the symptoms may not be due to the specific toxins of the several diseases in the course of which the state may develop. But, on the other hand, the similar, or even identical clinical characters, manifested in the very different diseases, suggest the real cause to be something other than the specific toxins, and that the poisons are to be found in the perverted tissue action or retained and altered products of tissue waste which the primary diseases have severally determined. How far the kidney is responsible for the defective elimination of the noxious agents is uncertain, but there is good reason to believe that the renal epithelium suffers from the toxæmia, and when damaged its excretory power is presumably deteriorated.

Prognosis.—The prognostic significance of this condition, whilst at all times grave, will in some measure be determined by the nature of the affection in the course of which it has been developed. Should the disease be one of a limited duration, such as an acute infection, it may be possible to tide the patient over until the crisis

occurs ; and though the onset of the state in the second week of typhoid fever would be almost certainly fatal, it is not necessarily hopeless should it develop towards the termination of the malady. The character of the pulse is probably the most reliable indication of the severity of the state, and more importance should be attached to that sign than even to apparently more serious nervous and muscular symptoms. In proportion as the pulse is soft and dicrotous will be the gravity of the case, and at the same time will be the greater need for **treatment** by stimulants, alcoholic and other. If the administration of these drugs effect no improvement in the vascular tone, the outlook is increasingly bad ; but a firmer pulse, and especially if this be maintained, is distinctly hopeful, and no effort should be spared to bring this about. Subcutaneous injections of liquor strychninæ (m. ii.-iv.) at intervals of four to six hours are often helpful ; digitalis and strophanthus by the mouth, with brandy or ether and ammonia, given as the pulse warrants, may successfully bring a patient through. The distaste for food adds to the difficulty, but such peptonised milk as can be introduced, whether into stomach or rectum, should be given. It may be well to give a grain or two of calomel if the bowels be constipated, and the state of the bladder should receive attention.

W. H. ALLCHIN.

RETROGRESSIVE CHANGES—NECROBIOSIS

Given the conditions of healthy nutrition, during the periods of growth and maturity, the living tissue elements maintain themselves, in virtue of their vitality, in a state of structural integrity with corresponding functional capability. This structural integrity includes not only what is recognised as histological characters, but also their chemical composition. Much remains to be learned concerning the latter, but provisionally at least a certain standard is accepted, and expressed as forms of proteids, of fats, of carbohydrates, and of inorganic substances. The composition of the tissues is obviously not unalterable. Associated with the manifestations of energy exhibited by the living body, its component structures undergo changes in composition as in molecular constitution, but in the cycle of normal metabolism these changes, with breaking down and waste formation, are as constantly renewed by assimilation and reconstruction.

Under certain circumstances, however, the structural (histological and chemical) completeness is not renewed, and departures from the normal to all degrees are to be found, although the very earliest and slightest shortcomings—which constitute the beginnings of disease—are undetected by our present means. To these defects in the chemical composition and microscopic appearances of the tissues, associated as they are with a deterioration in function, the term “retrogressive changes” is applied, the essential characters of which are a lowered chemical complexity of composition and an impairment of functional capacity.

The circumstances under which these changes are brought about are numerous and varied. Among the more important are imperfections in the quantity and quality of the necessary ingesta, solid, liquid, and gaseous, leading to defective nutrition; the directly damaging effect of poisons, whether mineral, alkaloidal, or microbic; the circulation of a deteriorated blood, as in anæmia, or a deficiency in the actual blood supply. In other cases the cause is to be found in some simple stimulation, such as pressure, or a more intense irritation, represented by inflammation. The cutting off of the direct trophic nervous influence by injury or disease of nerves or nerve centres leads to most marked retrogressive changes, which will more conveniently be considered subsequently (see Trophoneuroses, vol. iii.). A lack of the normal stimulus to nutrition supplied by healthy activity of an organ determines in varying degree a retrograde change in its structure. And, lastly, in addition to the foregoing, which may be denominated “secondary,” there is to be found inherent in the organism itself that inevitable

tendency to decay, and, finally, to death, expressed by the term senile change, which may be described as "primary." Thus linked on by insensible gradations to the normal course of life are conditions which constitute serious morbid states.

The intimate nature of these processes is obscure, and must be so until our knowledge of the chemistry of nutrition is more exact. In some cases the resulting changes consist in a distinct substitution of the cell protoplasm by other material, chemically less complex, functionally less capable; such are the true *degenerations*—cloudy swelling, fatty, colloid, mucoid, hyaline. Or the interstices of the tissues may come to be occupied by foreign substance, whether deposited therein from the blood, such as pigment or calcareous or uratic salts, or carried thereto by wandering leucocytes, or perhaps excreted from adjacent cells as results of perverted metabolism, as would seem to be the source of lardaceous material; all such changes are termed *infiltrations*. The simplest form of retrogressive change, involving amount rather than quality of tissue, is atrophy or wasting. Yet this is commonly associated with some of the other varieties, as they themselves usually occur in combination. Closely allied to these is that form of fibrosis which replaces other tissue to which it is often inferior in structural complexity and function, such as is seen in a wasting gland, or as a sequel of inflammation—fibroid substitution, as it has been termed.

These retrograde changes, transitional as they are between life and death, are fittingly expressed by the term *necriobiosis*, and are characterised in their functional aspect by defective and perverted performance. Tending as they do to the death of the region affected, this same end is more quickly reached by such tissue changes as are denoted by "gangrene," "caries," "coagulation necrosis," "liquefaction," etc., which are separable by no sharp line of demarcation from those more usually known as degenerations, but are associated with complete cessation of all vital phenomena. Only those changes which are of widespread distribution throughout the body, and are responsible for general or important manifestations, will be considered here.

ATROPHY

The special form of tissue involution denominated atrophy, consists in a diminution in the bulk, or in the number, or in both, of normally developed tissue elements. Dependent upon the cause it may involve the body generally, or some part only; and though not infrequently the only recognisable structural defect, is more often associated with some degree of fatty or other form of degeneration, with pigmentation, and with fibrous tissue replacement. The functional capacity of the organs involved will obviously suffer in proportion to the extent of the wasting.

Etiology.—The circumstances which lead to the occurrence of this

change are either a deficiency in the amount of nutritive material supplied, or a defect in the inherent assimilative power of the living tissue elements themselves ; or it may be that both of these conditions co-exist, inasmuch as the nutrition of those elements subjected to an impoverished blood supply will so far fall short that conceivably they may be supposed to be unable to make proper use of such aliment as may be furnished to them. Within the first category would be included those states comprised within the term starvation, whether due to an actual insufficiency of obtainable food, or to the existence of such diseases as prevent the digestion of the nutriment taken, such as stricture of the œsophagus or of the stomach, chronic vomiting, etc., or that interfere with the absorption of the digesta, as occurs in atrophy of the intestinal mucosa following on chronic catarrh of the bowel, or in diseases of the mesenteric lymphatic structures, both such potent causes of wasting in children. Or it may be that the food, sufficient in quality and quantity, has been properly digested and absorbed, but owing to perverted or excessive metabolism has failed to meet the requirements of the tissues, which have in consequence wasted ; such a condition is met with in diabetes mellitus, and in the course of fevers. Long-continued purulent discharges, and sometimes, but not always, repeated hæmorrhages, by diverting such nutriment as is taken, usually too little, determine a general wasting. Lastly, such conditions as diminish without completely arresting the blood supply to a part will bring about the same result, provided that the diminution be sufficiently long continued.

The causes of atrophy which may reasonably be regarded as referable to primary imperfections of the tissues themselves are those intrinsic tendencies which sooner or later lead to wasting, degeneration, and ultimately death, comprehended within the term senility, which, when prematurely manifested (unless in the case of the thymus in childhood, the uterus and ovaries at the climacteric, etc.), may be looked upon as disease, but otherwise are normally incident to vitality. Examples of inherent nutritional defects asserting themselves at different periods of life, and specially liable to be hereditarily transmitted, are seen in Friedreich's disease and pseudo-hypertrophic paralysis of Duchenne. Similarly some one or more of the tissues and organs may fail to attain the healthy standard of development from congenital defect, although to such the term atrophy is less correctly applied, the process being one rather of retrogression from a previously normally developed state. More important from the clinical aspect are those atrophies which apparently result from some failure in the trophic influence which is exerted on the tissues by the nervous system, whether this failure have originated in the higher centres, as it is presumed is the case in that remarkable condition known as *anorexia nervosa*, or in the cells of the anterior cornua of the spinal cord and their downward extensions, or by

cutting off the impulses from those centres by injury to the conducting nerves, or even induced, as has been suggested, in a reflex manner. The ill effect of the toxins of certain of the infective diseases on these so-called trophic centres should not be forgotten; and it may be that a similar cause determines the marasmus, often so extreme, which characterises inherited syphilis, and perhaps also the wasting influence of malignant disease may be partly ascribed to some toxæmia. Another and often occurring cause of wasting is the lack of that requisite nutritive stimulus represented by exercise and use; and as disuse may produce this result, so may prolonged overuse or abuse, well seen in the various muscular atrophies from "fatigue." At a certain point the hypertrophy which an organ exhibits in response to an inward call for exertion, fails, and atrophy follows.

Any organ or tissue elements subjected to pressure of a continuous character will almost certainly atrophy, partly from interference with the nervous and blood supply, and also from direct obstruction to the cell activities. Speaking generally, the more slowly any of these causes acts the more likely is atrophy, apart from degeneration, likely to result.

Investigation of these histolytic processes, as manifested in the normal disappearance of certain larval structures in lower forms of life, *e.g.* the tail of the tadpole, shows that the constituent cells of the tissues become less adherent to each other by a loosening of the cement substance, and at the same time the characteristic structure of the cell protoplasm is gradually lost by disintegration into a homogeneous material which no longer exhibits the power of staining with reagents. Liquefaction follows, and finally only a few granules are left, which are removed by phagocytes. In the course of the process the nucleus resists destruction for some time, but finally succumbs. A similar series of changes appears in muscle fibres, epithelial cells, and leucocytes, but it has been observed that morbid atrophies are sometimes associated with considerable nuclear proliferation which does not occur in the course of normal wasting.

Distribution.—The extent to which the various tissues suffer in the atrophic change varies in some measure with the cause. When a state of virtual starvation exists the adipose tissue especially wastes, being diminished by nearly 90 per cent in extreme cases, the spleen, pancreas, liver, heart, systemic muscles, skin, kidneys, and bones diminishing very much in the order stated; of all structures the nervous suffers least. The process is not confined to the normal tissues, since new growths may undergo atrophy, as occurs in uterine fibroids, and is then beneficial in character.

Characters.—Loss of bulk and weight are the essential features of the condition, but the affected organs are sometimes firmer from a fibroid substitution which has developed, as the essential elements—glandular, muscular, etc.—have wasted. For this same reason the actual

shrinking of the part may not correspond to the amount of atrophy of the cells or muscle fibres.

The most obvious appearances of wasting are those of the emaciation due to absorption of fat and consequent shrinking of the subcutaneous adipose tissue. Although this living of the body upon itself is likely to be of serious import, it is not entirely without some compensatory advantage, since as a consequence of loss of tissue there is a diminished area of systemic circulation, which is probably beneficial to a heart which shares in the general bodily enfeeblement, and at the same time may be supposed to thereby adjust the capacities of the pulmonary and systemic circulation to the benefit of the individual.

The indications for such **treatment** as is possible are to be found in the removal of the cause, an adequate supply of suitable nourishment adapted to the capacities of the patient, and the maintenance of tissue activities, by exercise, active and passive, massage and electrical stimulation.

FATTY DEGENERATION AND INFILTRATION

The conditions designated by these terms, although somewhat different in nature, are not always practically distinguishable, and, moreover, frequently coexist. Fat metamorphosis is the most widely distributed and most commonly occurring of the various retrogressive changes, and involving, as it does, many of the most important organs of the body, gives rise to clinical manifestations of considerable interest.

Pathology.—The development of an excessive amount of fat in regions where it is usually to be found, or its presence in tissue elements—cells and fibres—where it is not of normal occurrence, opens up the question of the actual source of fat and the theory of lipogenesis. It has been shown that the fat of the body is capable of being formed from the proteid, from the fat, and from the carbohydrate ingesta, though it is from the last named that by far the greater amount is derived.

The conversion of the proteid material of the food or of a gland cell or muscle fibre into a non-nitrogenous substance or fat, appears to be by a splitting of the molecule into a nitrogenous (urea or allied body) and a non-nitrogenous (fat) complex of atoms, and the removal of the former. Under conditions of healthy metabolism the end products are urea (and allies), carbonic acid and water, but should there be a deficiency of oxidation, then fat will result in place of the two last; and it is a deficiency of oxidation which is an essential in morbid fat formation. Such a change as this is clearly one of retrograde metamorphosis or true degeneration.

Whether the fat constituents of the food go directly to form the fat of the tissues is a little uncertain; they undoubtedly undergo a splitting up in the course of digestion and reconstitution during and after absorption.

The appearance of oil globules in the liver cells after a meal containing fat suggests the direct deposition (infiltration) of this substance from the blood, although the same phenomenon is also witnessed after a meal of carbohydrate food. There is some reason to think that a true infiltration of fat does not occur, and that fat formation is always due to proteid degeneration or to carbohydrate conversion, the fats absorbed becoming oxidised, and to that extent saving the nitrogenous tissues. Upon the settlement of this question, at present *sub judice*, the reality of infiltration as a process must depend. That the carbohydrates are the most abundant source of fat in the tissues is undoubted, though the exact chemistry of the change or precise site thereof are equally unknown.

EtioLOGY.—Like atrophy, fatty degeneration has its counterpart in normal life, as may be seen in the formation of milk in the mammary gland during lactation, and in the muscle fibre cells of the uterus after parturition. Whether the appearance of oil globules in the connective tissue cells is of the same nature or is due to a deposition therein of fat from the blood can only be determined when the actual occurrence of such a deposition is known to take place.

As a pathological process fatty degeneration is very frequent; induced by conditions primarily intrinsic in the cells themselves, or by influences inimical to their nutrition brought to bear upon them from outside. Among the former are those states comparable to senile change but of premature occurrence; whilst the latter are represented by such circumstances as interfere with proteid metabolism: (*a*) by imperfect oxidation of the nitrogenous material, fat rather than CO_2 and H_2O being formed. Such diseases as lead to a lessened intake of oxygen, *e.g.* pulmonary phthisis, or are characterised by a deficient oxygen-carrying blood, such as the anæmias, are apt to lead to fatty accumulation in the liver, in the heart, or in the subcutaneous connective tissues.

(*b*) Insufficient nutriment as a cause of fatty degeneration is seen in almost all cases, and whatever the tissue, when the normal blood supply is restricted without being entirely cut off, and is closely associated under these circumstances with atrophy. An actual diminution in the food taken below what is required less directly leads to this result.

(*c*) The destructive effects of such poisons as phosphorus, arsenic, alcohol, and certain bacterial toxins, especially that of diphtheria, are clearly manifested in the fatty degeneration undergone by the cells of the liver and kidneys and cardiac and voluntary muscle fibres. Similar changes are to be seen after pyrexia. The tissue degeneration associated with inflammation is mainly fatty in character.

(*d*) That want of exercise with over-feeding is a potent cause of fat accumulation is well known, and what is true of the body as a whole also applies to such individual parts or tissues as may be similarly cir-

cumstanced. The lack of stimulus to normal metabolism, with excess of nutriment, lead to a less complete oxidation of the tissues and consequent fat production. The fatty degeneration of paralysed muscles, and the so-called hypertrophic muscular paralysis, illustrate local affections of this kind.

(e) Fatty, together with atrophic, changes take place in tissues cut off from their trophic centres.

Distribution.—No tissue can be said to be wholly free from liability to this change, except perhaps the red corpuscles of the blood, although some are more prone than others. Dependent upon the cause, the condition may be general or local. The cells in which fat is of normal occurrence are the ones most likely to exhibit the change first and to a greater degree; such are those of the subcutaneous, sub-peritoneal, and intermuscular tissue, but that which is interstitially distributed, especially in the heart and voluntary muscles, is very soon involved, and may proceed to a considerable degree before the fibres themselves show signs of degeneration. To some extent, no doubt, the interference with the nutrition of the muscle which leads to the degeneration is in part contributed to by the pressure which this interstitial formation exerts. Among gland cells those of the liver are most liable, and next in frequency is the renal epithelium. Nerve cells and the axis cylinders and myelin sheaths of nerve fibres may all become the seat of fatty degeneration, the fat in such cases being probably derived in great measure from lecithin.

The arteries are specially prone to undergo this degeneration either as a part of a general senile change, or as a stage of atheroma, or as a primary affection of the endothelial and subendothelial connective tissue cells of the large arteries.

But the change is not restricted to the normal tissues; new growths and migrated leucocytes may equally suffer, in the latter contributing to the formation of pus.

Characters.—Tissues and organs, the seat of fatty degeneration or infiltration, are usually more bulky and softer than normal, and oftener of a paler colour, uniformly or in patches, presenting appearances to which very fanciful names have been applied. On section the surface appears greasy, and in extreme cases the tissues may burn with a smoky flame.

Microscopically, the cells and fibres involved are seen to have lost in a varying degree their characteristic structural appearances, striation and other features becoming less distinct, or completely disappearing. The tissue elements are occupied by dark highly refractive granules or minute globules, with which they may be entirely filled, the latter perhaps fusing into a single drop, which may obscure the presence of the remains of the cell protoplasm and its nucleus. The fat granules are turned black by osmic acid, and are dissolved with ether, but are

unaffected by acetic acid, which clears up those of an albuminous nature.

Although in general the functional capability of organs and tissues so affected is diminished, it is none the less true that in certain structures, *e.g.* the liver, the change may be considerably advanced, and but little interference with their activities be manifest. Not so, however, with such organs as the heart or nervous system, where enfeebled and irregular action soon follows on the establishment of degeneration. The facility also with which this morbid state can be recovered from, assuming that the cause is removed, seems to depend in great measure upon the extent to which the cell protoplasm has been destroyed, and it has been held that these differences justify the view of the occurrence of a mere deposition distinct from actual degeneration.

Under favourable circumstances the fat which loads the cells and fibres may become absorbed, and the parts regain more or less their normal condition, perhaps with some shrinking, unless the essential elements have been completely destroyed. Or the absorption may only be partial and mainly concern the fluid part, leaving the fatty matter to undergo a cheesy transformation, to which the term "caseation" is applied. Though not restricted to, this change especially takes place in, tuberculous growths which have become fatty from inanition. Crystals of cholesterine and of the fatty acids may be found in the mass, which tends either to break down and liquefy and so become removed, or to become the seat of deposition from the blood of earthy salts and of calcification.

The condition is not susceptible of treatment, except so far as the removal of its cause is possible in any given case.

LARDACEOUS DEGENERATION

This variety of retrograde change appears to be less an actual conversion of the tissue elements themselves than a deposition in the connective tissues of a proteid material, which is not a normal constituent of the body; probably derived from a perverted metabolism in certain cells, glandular and lymphoid, which primarily at least are not involved in the change, though they become atrophied and the seat of fatty degeneration from the mechanical pressure to which they are subjected by the infiltration, and by their impaired blood supply.

Pathology.—The precise nature of the change, as well as its immediate causation, is obscure; nor is much information on this point to be obtained from a consideration of the morbid conditions with which it is associated. Of these by far the most constant is chronic suppuration, especially of the bones, and pulmonary phthisis, where the destructive process is accompanied with much pus discharge. Much less often, though still with considerable frequency, comes acquired syphilis

as an antecedent or perhaps coincident condition. It is quite as a late phenomenon or even perhaps as a post-syphilitic manifestation that lardaceous degeneration is met with, and its occurrence in the course of hereditary syphilis is very doubtful. Sometimes none of these conditions are to be found, and no cause whatever is apparent.

The preponderant association of lardaceous degeneration with infection by pyogenetic organisms has suggested attempts to produce it artificially by repeated inoculation with these microbes, especially the staphylococcus pyogenes aureus. So far the results are not quite conclusive, although in some animals so treated the organs showed the characteristic tests of lardacein. On the whole it seems highly probable that the normal metabolism of certain cells is altered by some toxins, most likely of microbic origin, the outcome of the perverted process being the lardacein, which is excreted from the cell into the interstitial spaces, perhaps also at times being retained in the cell itself.

This affection is most usually met with between the ages of twenty and forty, and is rarely seen under ten years. On the whole it is of commoner occurrence in males.

The substance which infiltrates the tissues—*lardacein*—is a proteid material that is not obtainable from healthy tissues, in this respect offering a marked contrast to fat. In chemical composition it is distinguished from albumens by containing rather less nitrogen; and the tissues occupied by it yield much less potash and phosphates, but considerably more earthy salts than are to be obtained from the corresponding healthy structures. It is insoluble in water, in dilute acids or alkalies, and in saline solutions, but is dissolved by strong acids or alkalies becoming converted into acid or alkali-albumin; it is also very resistant to the action of the gastric juice.

Two very characteristic *tests* are applicable for the detection of this material. A watery or alcoholic solution of iodine poured over a clean-cut section of a lardaceous organ will stain the substance a deep mahogany brown, the normal tissue taking a pale yellowish tint. (Subsequent treatment of the stained areas with dilute sulphuric acid will alter the brown into a bluish-black colour, which led to the erroneous supposition that the substance was of a starchy nature, and hence the name “amyloid” was improperly applied to it.) For microscopic sections a solution of methyl-violet is used, which causes the lardaceous material to assume a rose-pink colour, the unaffected tissues becoming blue.

It may be observed that occasionally organs are found presenting all the naked-eye and microscopic appearance of lardaceous change and yet failing to exhibit the characteristic colour alterations with iodine and methyl-violet, and it seems probable that lardaceous degeneration is allied to, though distinct from, such forms of retrogressive change as are described by the terms “colloid,” “mucoid,” “hyaline,” etc., in

which the normal proteid substance of the tissues is replaced by other nitrogenous bodies of a retrograde character and deteriorated functional capability. Moreover, the true lardaceous substance sometimes undergoes a further change into substances to which these terms may be properly applied, suggesting thereby some common inter-relationship.

Morbid anatomy.—The organs most frequently affected are the kidney, spleen, liver, and intestines in that order; the stomach, suprarenals, heart, and lymphatic glands much less often, and the pancreas, thyroid, testes, and voluntary muscles very exceptionally, and the nervous tissue probably never. It is seldom that one organ alone is involved, the first mentioned being all more or less attacked if the disease have lasted for long. Owing to the addition of a large quantity of new material the organs are much increased in bulk and weight, sometimes to three or four times the normal; they are firmer, less elastic, and present in section either a uniformly smooth and somewhat glistening homogeneous “waxy” appearance, or these characters are limited to certain areas. This latter condition is especially well seen in the spleen, in which the change may be restricted to the Malpighian bodies, which appear as semi-translucent deposits scattered through the section, which have been compared to “boiled sago” grains; or the change may be diffuse, the entire viscus being involved. In the liver, the middle zone of the lobules is first and perhaps only affected, though later the degeneration may extend to the other regions. Very frequently the change may be so inconsiderable as to be unrecognised without the application of iodine or microscopic examination.

In all cases it is found that the alteration commences in the small arteries and capillaries (a fact which has been urged in support of the toxæmic nature of the cause), taking place in the intima and media, leaving the endothelium unaffected and seldom extending into the adventitia. Later the interstitial tissues of the organs in which those affected vessels run become infiltrated with patches and streaks of the homogeneous-looking substance which, eventually increasing, obliterates the normal tissue elements and forms a uniform structureless mass, in which the atrophied remains of the cells and fibres can with difficulty be seen. Associated with the change is usually more or less fatty degeneration, and frequently some fibrosis as well. In the kidney portions of the material may be extruded into the tubules, giving rise to casts which pass into the urine.

Clinical characters.—No very definite symptoms can be set down as peculiar to this condition. It is certain that it may proceed to a very considerable extent without its presence being suspected. The enlargement and increased firmness of the affected organs may be detected in the ordinary course of physical examination, but seldom, if ever, is pain or tenderness complained of. The symptoms of hepatic or splenic involvement are singularly negative apart from the physical

signs. But the degeneration of the kidney leads to severe albuminuria, and the change in the intestinal mucosa is marked by diarrhœa. The frequently occurring ascites and œdema may be in great measure ascribed to the changes in the vessels. How far some general symptoms, such as anæmia, wasting, and debility, are referable to the disease upon which the degeneration is consequent is not always easy to decide, but it is rather as contributing to a fatal issue than as a distinct cause of death itself that the condition is to be regarded. Such special clinical features as the affected organs may severally exhibit will be further described under their respective headings.

Treatment.—The condition is beyond treatment by drugs, but owing to its comparatively harmless character, very considerable benefit will follow even in most advanced cases if the cause can be removed. Hence operation for the cure of suppuration should not be refused on the ground of the presence of extensive lardaceous degeneration, although improvement is not so likely to ensue if there be evidence that the kidneys are much involved. Considerable diminution in the size of the liver has frequently been noticed under such circumstances.

SENILITY

Why, when a living organism has reached its full stage of development it should decline in structural completeness and deteriorate in functional capability until it ceases to live is one of the most obscure problems of biology, but that it is inevitable is a fact of universal experience. To this period of decline the name "senescence" or "senile involution" is given, and it is to be regarded as a normal stage in the life-history of the organism, marked by its own peculiar characteristics, just as the stages of growth and differentiation, or of maturity, exhibit their distinguishing features.

Without attempting to discuss the various theoretical explanations that have been suggested for the onset of decay and death, explanations which involve the consideration of the correlative questions of the origin and the nature of life, it may be desirable to point out that the essentials of "growing old" consist in a gradual diminution of those material interchanges which underlie the manifestation of the living energies, in a loss of the reproductive faculty, and in a failure of the sensori-motor relationships of the individual to his surroundings, which together make up the vitality of the higher organisms. In the human being this state is usually reckoned as being established at the age of seventy years, though its onset may have been recognised for a decade previously. Occasionally it is clearly premature in manifestation, and then may be the result of heredity or of prejudicial influences that have been acquired, and as such might be considered as morbid.

Anatomical characters of senility.—The special structural

changes which characterise a normal senescence are a progressive atrophy or simple wasting of tissues with some associated degeneration, chiefly fatty, and infiltration of calcareous salts. Together with this wasting, there is also in certain organs an over-formation of fibrous tissue. No general statement can be made as to the extent to which either of these alterations may proceed; the widest variation is met with, but much or little is to be found in every old person. It may be observed that those tissues which exhibit the highest grade of structural differentiation and specialisation of function, as for instance the nervous and muscular (in which one of the fundamental properties of bioplasm, the power of self-multiplication and regeneration, is sacrificed with the gain of a higher degree of perfection attained in other directions), exhibit the changes of senility sooner and more completely than do those which are more mechanical in function and whose living elements present less departure from the embryonic type.

The body weight is diminished, except when there has been a considerable increase in the fat at the climacteric, when the total loss of weight may be inconsiderable. The several organs and tissues with scarcely an exception present a *wasting* to some extent. This is particularly observed in the nervous and muscular tissues, the skin and mucous membranes, the glands, secretory and lymphatic, and the generative organs.

“A most important change, and one that exerts a very direct influence on tissue nutrition, is an extensive shrinking or even obliteration of the capillaries in almost all the textures. The skin becomes much diminished in thickness, especially in the papillary layer, the constituent papillæ being very indistinct; and loss of hair and change in its colour are well-known features. The senile changes in the skeleton are of peculiar interest. The bones, which in the earliest stages of formation are solid, become, as development proceeds, hollowed internally, by the formation of cancellous tissue and, in the long bones, of the medullary canals. As the absorption of the central part proceeds, the bones nevertheless increase in weight and bulk until maturity is reached, by sub-periosteal ossification; but in the decline of life, as this process takes place scarcely at all, and the atrophy continues, the bones, whilst retaining their general size and form, become much thinner, lighter, and weaker. The change takes place especially in the cancellar parts, which are most vascular, and where the agents for absorption are most active—hence the special weakness of the ends of the long bones, and their liability to fracture. The alveolar parts of the upper and lower jaw bones, consisting as they do chiefly of this loose spongy tissue, are characteristically wanting in the aged; and since these parts carry the teeth, this atrophy of the bone leads to their falling out. The lower jaw is one of the few bones in which an alteration in shape takes place, the ramus and body coming to be more nearly in a straight line, with

proportionate widening of the angle. The bone thus resembles the shape it has in the infant, with the difference that it then consists mainly of the alveolar part, whilst in old age it is the denser basal or sub-alveolar part that alone remains. The altered shape of the mandible has been attributed to the loss of teeth causing a deviation in the line of action of the masticating muscles. The late Sir George Humphry found as the result of extensive investigation no confirmation of the commonly accepted statement that the angle beneath the neck and shaft of the femur becomes smaller with age. The same observer has drawn attention to two exceptional conditions of an opposite character met with in the skull. One of these occurs as nearly symmetrical areas of atrophy of the outer table and diploë, forming well-marked depressions extending obliquely across the parietal bones, which he is inclined to attribute to 'the pressure of the occipito-frontalis tendon stretched upon, and playing over, the most prominent part of the vertex.' The other condition he has described as a considerable thickening of the calvaria, especially towards the frontal region, with great density of the bone. The explanation of this very anomalous state, so contrary to what takes place in the cranium and entire skeleton generally, is not obvious. The age at which these changes in the osseous system set in is very variable, but they commonly commence earlier in women than in men. Slight atrophy takes place in the cartilages, costal and articular, the latter accounting for the diminution in height of the old person. Corresponding to the loss of strength in the bones is an increasing weakness in the power of the muscles, which explains, *inter alia*, the fact that fracture by muscular action is no more frequent in the aged than at other periods of life. It is to the weakening of the dorsal muscles that the stoop of age is attributable."¹

As illustrative of the *degenerative changes and infiltrations* may be mentioned the arcus senilis, atheroma and calcareous change in the vessels and cartilages, fatty degeneration of the cardiac muscle: all very variable in the extent to which they may be developed, but equally expressive of a diminished nutrition determined by an impaired blood supply, an impoverished blood, and an intrinsic failure in the vitality of the living elements of the tissues.

The *fibrosis* which occurs in the course of normal senile involution is in part no doubt of the nature of a substitution, replacing in some measure the wasted tissue elements of higher grade, nervous, muscular, etc. But in two situations, viz. in the arteries and in the prostate, an extensive increase takes place in the fibrous tissue which adds considerably to the thickness and bulk of these structures. A senile fibrosis of the kidney and of the testis is also recognised, and the capsules of liver and spleen are sometimes thickened from the same cause.

The *blood* in the aged is diminished in quantity, deficient in

¹ Article "Senility" by present writer in Quain's *Dictionary of Medicine*.

corpuscles, and is of a lower specific gravity, and said to be less coagulable.

Physiological characters of senility.—"The results of such structural imperfections appear in deterioration of the purely physical, as well as of the specially vital, properties of the tissues. There is an increased rigidity in some parts, as the tendons and blood-vessels; and a diminished cohesion in others, as the nails and bones, which are brittle and easily broken. Perhaps the most prominent and distinguishing mark of old age is a loss of elasticity; the skin, cartilages, blood-vessels, and lungs show this to a very marked extent, in the wrinkled integuments, dilated vessels, and distended air cells. It has been noticed that this vascular dilatation particularly affects the thin-walled veins, and more especially those which do not run with arteries, are more superficial in position, and are concerned less with nutrition than with the proper return of blood—the 'derivative circulation' of Sucquet. The advantage of this is apparent, for such an arrangement must be a safety valve in the case of the brain, to which organ there is a liability to determination of blood, and where the vessels are apt to rupture; hence the frequent turgescence of the nose and ears, and development of the veins of the diploë, in the aged.

"The muscular contractility and nervous irritability are diminished; and atrophy and degeneration of the gland cells lead to failure in their powers of secretion.

"The heart's beat is weak, and frequently intermittent, from defect in rhythmical nervous stimulation; the cardiac sounds are feeble and often altered; and there is a general tendency to venous congestion. The pulse is often full and of high tension from fibrosis of the arteries affording a fallacious appearance of strength. Its mean rate after the age of sixty-five years is 75, gradually diminishing to 70.

"The tissues, which differ in chemical composition from those of mature life, must in their metabolism form different products of waste; whilst the altered blood, circulating in a restricted area with diminished force, must offer to the organs a different pabulum from that which they have hitherto received, supplied as it is by impaired digestive organs. The enfeebled respiration prevents complete oxidation; and the excretory organs, being less capable, imperfectly withdraw from the body the results of metabolism. The quantity of urine is often diminished to fifteen or twenty ounces *per diem* in old men enjoying good health. It contains a total amount of solids less than the normal standard, but the urine itself may be relatively of higher specific gravity, and deeper colour, from its diminished quantity.

"As the nutritive functions fail, so do those of the neuro-muscular system. The sense organs imperfectly receive impressions, which are but dimly communicated to the sensorium, whence feebly emanate the impulses needful to determine movements in muscles, the contractility

of which is gradually diminishing. Meanwhile, the higher mental qualities, such as memory, judgment, and reason, dependent as they are upon the most perfect nutrition, gradually fail. The opposite conditions of wakefulness and drowsiness are frequently met with, and seem to be due to brain-wasting, as well as to some change in the cerebral circulation. To the same cause may be attributed the restlessness which is frequently met with.

“As a further manifestation of the lowered vitality, recent careful and continued observations have shown that the average body temperature is slightly lower than it is in adult life, and the ability to resist cold is diminished.

“The power of reproduction, lost by women at the climacteric, before the stage of senility sets in, is occasionally preserved by men to an advanced age.

“Thus the old man presents a strong contrast in his vitality to that of the child; for whilst the life of the latter is so largely dependent upon, and so readily responsive to, external or peripheral impressions, the former lives more and more within himself; the distinctive animal functions gradually failing, as his existence becomes restricted to the performance of those of self-nutrition. The progressive impermeability of the capillaries, and the lessened vitality of the skin, alike tend to withdraw from the surface towards the central organs the manifestations of life.”¹

Diseases of old age.—Old age as such is not to be looked upon as disease, but inasmuch as the power of tissue resistance at that time is diminished, the liability to disease of certain kinds is increased, and owing to the alteration in the tissues and organs the symptoms of illness when it supervenes are likely to differ from those of the same malady occurring in early or adult life. Hence it is frequently difficult to draw the line between those changes which are normal to old age and those which more properly are to be considered as a disease of that period, especially since an excessive or disproportionate degree of atrophy, degeneration, or fibrosis may be looked upon as morbid. “Death from old age, when the organs have gradually and uniformly failed, is not unknown, but the fatal end is more commonly due to some disease, which has either lasted from an earlier period, or is especially the acquirement of this stage.

“The maladies particularly characteristic of old age are marked by certain general features, which they owe to that condition of nutrition in which the tissues are at this period. Thus, as a rule, they present but little activity in their progress, or but slight severity in symptoms, though they are none the less likely to bring about a fatal result, from the ill-resisting power of the whole system. Diseases of an acute character are rare at this time, and such as do occur assume an

¹ *Loc. cit.*

adynamic, and even apyrexial, form, and are very liable to run a most insidious and latent course. When once established, an illness tends perhaps more towards maintaining an isolated attitude, without those sympathetic disturbances of many other organs so pre-eminently the case in children. The power of reaction possessed by the aged is but very slight; owing to this, diseases readily lapse into a chronic state, or even present a chronic character from the outset, whilst comparatively trifling causes may lead to serious results. The observations of Sir George Humphry, however, go to show that the reparative power in persons of even advanced age is often greater than is supposed, and he adduces well-authenticated cases of complete recovery from severe accidents and illnesses; and in such we may reasonably infer that the degenerative changes are wanting or but very slight.

"There is probably no single disease which is met with in advanced age only; rather is it the case that many diseases which prevail at certain periods of life are wanting in old age. The atrophy of every tissue and organ entails a general failure in function; and should this failure predominate in any one system, as may readily follow from a marked degeneration of certain special parts, we have some exception to what may be taken as the normal standard of the senile state, and therefore a disease of it. The same difficulties surround the question, why one set of organs should be affected rather than another, as at other ages; but there nevertheless does exist a preference towards affections of the circulatory, respiratory, and nervous systems. But a very large proportion of old people are entirely free from disease—of 824 persons over eighty years old, 55 per cent of the women and 35 per cent of the men were reported to be healthy"¹ (Humphry, *Collective Investigation Records*).

It is clear that this stage of life no more demands treatment than does any other period. But it has long been the object of human endeavour to avert it as long as possible and to mitigate its effects; and for the attainment of longevity many means have been proposed, though as yet without any reliable result. Among the more recent plans proposed is that by the late Dr. Brown-Sequard, who regarded senescence as attributable to the loss of influence exerted on the tissues generally by some internal secretion of the reproductive glands, the loss following from wasting of these organs. He recommended subcutaneous injections of extracts of these structures, but it cannot be said that any definite success has attended their use.

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¹ *Loc. cit.*

PROGRESSIVE CHANGES

HYPERTROPHY

The condition so denominated consists essentially in an increase in the bulk of an organ or tissue due to an overgrowth of its normal constituents. This overgrowth may, and usually does, involve a numerical increase—hyperplasia—as well as an individual enlargement of the tissue elements.

Much difference exists among the living cells of the body as to the extent to which they proliferate in the course of a healthy existence. For whilst the epithelial cells of the mucous and cutaneous surfaces and of glands like the mamma are constantly being thrown off and renewed, such specialised structures as nerve cells and almost, if not quite, as certainly muscle fibres, exhibit a stability and permanence when once they have been formed in the early stages of tissue differentiation, and in normal circumstances are not periodically shed and replaced; nor do they proliferate under the influence of morbid stimulation. The occurrence of hypertrophy in great measure conforms to this, but not entirely so, for although an overgrowth of nerve cells or fibres is almost unknown, muscular hypertrophy is frequent. Speaking generally, the various members of the connective tissue series, such as fibrous tissue, adipose tissue and bone, are very prone to become hypertrophied, as also is the case with such glands as the kidney and to a less extent the liver, the cells of which ordinarily exhibit but little tendency to proliferate. The source of the new cells in these organs is not clearly ascertained.

Representing as it does the result of over-nutrition, the conditions upon which hypertrophy depends are modifications of those to which the normal growth and nutrition are due. For its efficient production and maintenance an increased blood supply with an excess of nutriment is requisite; but this condition alone will not determine a hypertrophy unless the living tissue elements themselves be disposed to over-formative activity. What may be the stimulus to the increased capacity for growth on the part of the cells is unknown, conceivably it may be a neurotrophic influence, or some products of the metabolism of other tissues (internal secretion). The demand for overwork on the part of the tissue is a well-recognised cause of its hypertrophy, but the extent to which this may act is limited; that is, the tissue can only respond to this stimulus to a certain extent. Such as it is, however, it is the response under these circumstances which gives the chief interest and importance to hypertrophy from a clinical point of view. When from any cause the efficiency of one of certain double organs (*e.g.* kidneys) is diminished,

or a greater call is made upon a structure, such as the heart to overcome an obstruction in the circulation, then hypertrophy develops in the sound organ, or in the heart, whereby compensation is effected and the shortcoming is made good. Under normal conditions the tissues maintain their structural integrity without exerting their functional capacity to the full; they possess a margin of "reserve power" which may be called upon, and that underlies all compensatory effort. With age this adaptability to environment progressively diminishes, and as it becomes exhausted compensation fails.

The remarkable hypertrophy which may involve the whole body, as in gigantism, or special regions, as in acromegaly, leontiasis ossea, etc., would appear to be essentially dependent on an increase in the growth capacity of the tissues called forth by some alteration in their mutual relationship, such as the formation of certain metabolic products or an internal secretion (? of pituitary body), or some perverted neurotrophic influence, or the removal of a natural resistance between the tissues (tissue tension) which has been supposed to exist. The view has also been held that such overgrowths are due to "embryonic remnants" in the tissues which possess a marked power of proliferation. It is noticeable that the bones and other forms of the connective tissues especially exhibit the excess in growth; indeed a fibrosis, or over-formation of fibrous tissue, is one of the most frequently occurring and widely distributed hypertrophies, and occasionally seems to be determined by a continued hyperæmia only.

W. H. ALLCHIN.

INFLAMMATION AND ITS SEQUELS

It is probable that inflammation, being the commonest and most variable of all pathological processes, was the first to attract the attention of workers in medicine. At any rate the subject was exhaustively dealt with by Hippocrates (B.C. 430), who described it under the name “*φλεγμονή*,” which still survives in the term “phlegmonous erysipelas,” and by Celsus (A.D. 32), who recognised that the four “cardinal signs” of the condition are *rubor, calor, tumor, dolor*. To these a fifth—*functio læsa*—was added, but only many centuries later.

PHENOMENA OF INFLAMMATION AS OBSERVED IN THE FROG

The phenomena of inflammation have been studied experimentally both in warm and in cold-blooded animals, and have been found intrinsically the same in both classes. Without going into details as to the method of procedure, it may be said that if the mesentery of the living frog, after being slightly irritated, be examined microscopically, the following series of changes will be observed. After a momentary and passing constriction has taken place, there appears an obvious dilatation of the blood-vessels, and many capillaries not previously visible come into view. All these vessels are filled with blood, which, owing to the dilatation, courses through them far more rapidly than normal. After a certain length of time, which varies indefinitely according to the degree of irritation and other circumstances, the rate of blood-flow slackens, so that now individual corpuscles can be recognised as they pass along the blood channels; but the vessels still remain dilated. The slowing of the blood-flow still continues, until at length the blood comes to a standstill in the vessels immediately beneath the point of maximal irritation. At this time it is possible to recognise three concentric areas: (1) a central focus of *stasis*, in which the vessels are dilated, but in which there is no circulation; (2) a zone lying around the region of stasis, in which the vessels are dilated and in which the circulation goes on sluggishly; and (3) a zone lying outside both of these, in which the vessels are dilated, and in which the circulation is more rapid than normal. These areas shade into one another, and around them all lies the normal tissue with a normal circulation. The vessels in the central area in which there is stasis show a peculiar appearance, because they seem to be converted into solid homogeneous cylinders in which no trace of individual corpuscles is recognisable. At the first glance it might be imagined that the blood within them has coagulated, but that stasis is not coagulation is shown

by the fact that if the effects of the irritant have not been too severe and pass off, the apparently homogeneous cylinders again break up into the constituent corpuscles and these return into the circulation. It is of course unnecessary to state that with a more severe irritant definite coagulation may be produced and that resolution of this condition—which is a variety of death—is impossible. Besides these changes, which are very obvious, other phenomena may be observed. In those regions where the rate of blood-flow is diminishing, one of the most noticeable changes is a disappearance of the normal differentiation of the column of blood in a vessel into the axial and the plasmatic layers. This indeed is the direct result of the diminution in velocity of the blood-flow, but it is of the highest importance in bringing about other changes which will now be considered.

Under normal circumstances the plasmatic layer is almost cell-free. At most, here and there, it contains a colourless corpuscle which has been driven against the vessel wall by its lower specific gravity. But directly the flow of blood begins to slacken in the vessel, and long before there has ceased to be a differentiation between central and plasmatic layers, the number of leucocytes in the plasmatic layer is seen to be markedly increased. Moreover, the leucocytes seem to cling more closely to the vessel wall than normally, and often they cohere and form small masses. While recognising this fact and directing attention to the plasmatic layer and the vessel wall, it will probably be seen that a small knob of colourless protoplasm makes its appearance on the outside of the vessel wall—usually a capillary or small vein. This knob of protoplasm increases in size as it is watched, and ultimately separates from the vessel wall and travels by amœboid movement to a short distance therefrom. It is a living leucocyte which has *migrated* through the vessel wall. As time passes numbers of these migrated leucocytes are found on all sides of the vessels. If special precautions are taken it will further be noticed that the surface of the mesentery, which, when first drawn out from the abdomen was almost dry, has now become covered by a number of droplets of fluid. This fluid, which is highly albuminous, is in reality derived from the blood plasma.

The phenomena, therefore, which may be observed in such an experiment are, (1) dilatation of blood-vessels with acceleration of blood-flow; (2) dilatation of blood-vessels with slackening of blood-flow; (3) stasis; (4) migration of leucocytes; (5) exudation of fluid from the blood-vessels. All of these are brought about by the action of an irritant, and are the invariable fundamental essentials of inflammation. It must not, however, be supposed that they follow one another in the orderly sequence given above, for slackening of blood-flow, migration, and exudation of fluid are of course synchronous, and at the same moment the picture will vary according to the portion of the field examined.

Though the red blood corpuscles form by far the most numerous

element in the circulation, it is generally allowed that they play a merely passive part throughout. When the irritant has been of a sufficient degree of severity they may be found outside the vessel walls, but they do not pass out by their own active movements, as is commonly held to be the case with migrated leucocytes, but are thrust out, either through an actual rupture in the vessel wall, or through normal but dilated openings (stomata) therein, or possibly through the anatomically intact wall, by the pressure within the vessels. Extrusion of red blood corpuscles in this manner is termed *diapedesis*. Nor do red blood corpuscles, when diapedesis has occurred, travel by their own movements to a distance. They remain immediately outside the vessel wall, or if removed to a distance are passively carried by the lymph or by leucocytes which englobe them. Leucocytes, on the other hand, may travel to a considerable distance from the vessel from which they migrated by their own amœboid movements.

CARDINAL SIGNS OF INFLAMMATION

It has already been said that to the four cardinal signs of inflammation—redness, swelling, heat, pain—as originally given by Celsus, a fifth—impairment of function—was subsequently added. We may now endeavour to explain these by the light of the phenomena which have been described in the last section.

The *redness* is obviously dependent directly upon the congestion which obtains in an inflamed part. That this is considerable has long been known, and Cohnheim found by direct measurement that the amount of blood flowing in a given time from a cut vein of an inflamed dog's paw is about double that which flows in the same time from the corresponding vein in the sound paw. So considerable is the vascularity and so rapid the flow of blood through the dilated vessels around the focus of inflammation, that the blood in veins from an inflamed part is often of a bright arterial colour. This is, however, not always the case, for where there is obstruction to the return of blood in the veins (as around a varicose ulcer) the venosity may be considerable and the inflamed area around the ulcer may be purple in colour and not red.

The actual nature of the vascular change and the manner in which that change is brought about are subjects upon which little can be said with absolute certainty. That an irritant may cause definite structural changes in a vessel wall is generally recognised. But there is considerable uncertainty whether those finer changes which are associated with exudation of fluid and migration of cells are simply exaggerations of the changes occurring normally during functional activity of a part, viz. active congestion with increased output of fluid through the vessel wall, and increased flow of lymph from the part; or whether they are distinctly pathological and have no counterpart in physiological life at

all. Cohnheim inclined towards the latter view. He regarded the fact that leucocytes tend to adhere to the blood-vessel walls in an inflamed part as evidence of an increased "stickiness" of the vessel wall and as showing that it undergoes in inflammation a molecular change, which, though it may be unrecognisable anatomically, is recognisable functionally in all cases by its results, viz. exudation and migration. Most modern authors follow Cohnheim, but, as will be seen later, it is quite as possible that the altered behaviour of the leucocytes may depend upon changes induced in them as upon alterations in the wall of the blood-vessel which contains them.

With regard to the vascular dilatation, we are certain that it depends in some degree upon altered nervous action; we recognise that the local nervous mechanism in the small arteries is thrown out of gear by the action of the irritant. For if the vaso-motor nerves of a limb be cut, and the resulting degree of vascular dilatation be measured by means of the plethysmograph, it will be found that when inflammation is induced in the part the blood-vessels undergo a still further dilatation. But whether the vaso-motor centre and other parts of the central nervous system have a share in producing the vascular dilatation is a much more difficult question to decide: upon the whole it is probable that such is the case.

To digress for a moment, it may be well to mention that although the synonymous terms "congestion" and "hyperæmia" invariably mean that the parts concerned are fuller of blood than normal, they do not invariably mean that the same pathological process is at work. As a matter of fact several different forms of hyperæmia are known, of which the most important are (a) *active*, (b) *passive*, (c) *paralytic*, and (d) *hypostatic*. *Active hyperæmia* occurs when a part is the seat of functional activity or is subjected to slight external warmth. It is always accompanied by dilatation of arterioles and capillaries and often of veins, by an increased velocity of blood-flow through these vessels, by an increase of metabolism, and by an increased flow of lymph from the part. Thus when a muscle or salivary gland is exercising its function normally or as the result of experimental stimulation of its nerve, dilatation of its arterioles always takes place. As a result the capillaries are fuller than normal and the velocity of the blood-flow through them is greater—often, indeed, so much greater that the arterial pulse is carried through to the veins and the venous blood is arterial in colour. Moreover, direct measurement shows that there is a considerable increase of lymph formation. It is this variety of congestion which probably obtains in inflammation. *Venous* or *passive hyperæmia* is said to occur when the veins leading from a part are for any reason obstructed. The capillaries and veins are fuller of blood than normal, but the velocity of the blood-flow through them is diminished and therefore the blood in the region concerned becomes highly de-oxygenated and causes the part,

if superficial, to assume a purple hue (cyanosis). At first this form of congestion is unaccompanied by any alteration in the lymph-flow, but later lymph formation is greatly increased, and since the cause of obstruction to the veins is, as a rule, a cause of obstruction to the lymphatics, a large portion of the lymph remains in the serous cavities or in the tissue spaces, and leads to certain varieties of dropsy, œdema, or anasarca. In the case of internal organs, long-continued venous congestion causes atrophy of the essential cells of the part, and deposition in them of hæmatogenous pigment. Often, too, its occurrence is associated with a formation of new fibrous tissue. Such changes are well seen in "nutmeg liver" and "brown induration of lung." *Paralytic congestion* results whenever the vaso-constricting influences which normally reach the arterioles fail to do so owing to some interference (injury, tumour, etc.) with the vaso-motor tracts. Such congestion is of course arterial, but it differs from active congestion in that it is unaccompanied—at all events at first—by an increased flow of lymph, that it is independent of functional activity, that it is generally associated with lowered metabolism, and that it is frequently the cause of a fall in general blood pressure. *Hypostatic congestion* is of great clinical importance, as it frequently occurs in diseases accompanied by severe constitutional symptoms, and is often an important factor in bringing about the death of the patient. It is an expression of a feeble heart and toneless vessels, meaning as it does that the ventricular force is not sufficient to fully overcome the normal effects of gravity. It always affects dependent parts, and since the force of the right ventricle is normally less than that of the left, it most commonly concerns the lungs.

The *swelling* in inflammation is chiefly dependent upon the exudation poured out from the dilated blood-vessels, but is also caused in part by accumulation of migrated leucocytes in the tissue spaces, and in some degree by the over-fulness of the blood-vessels. Of the fact itself that in inflammation an excessive amount of fluid leaves the blood-vessels there is no doubt. Cohnheim found by placing a cannula in one of the lymphatics of the inflamed paw of a dog, that the amount of lymph flowing per unit of time may be increased to ten times the normal. But as to the way in which the fluid leaves the blood-vessels there is considerable divergence of opinion. It is undecided whether it is actively secreted by the vessel walls or whether it passes through them by a simple process of filtration. It is, moreover, uncertain whether—upon the filtration view—it passes through dilated stomata or through the bodies of the endothelial cells or through the cement substance between these.

The *heat* of an inflamed part is due to its increased vascularity. At one time it was supposed that an inflamed part can be hotter than the rest of the body, and this was regarded as dependent upon local

chemical changes. But it was found by more extended observation that though the temperature at the seat of inflammation may be—and commonly is—higher than in surrounding parts, it is never higher than in the deeper parts of the body. This indeed is what might be expected from our knowledge of “circulation times.” For any heat derived from local chemical changes must almost immediately be distributed over the whole body. Nevertheless the fact that the temperature of an inflamed part is never higher than it is in deep parts of the body, must not be taken to indicate the absence of chemical changes producing heat at the site of inflammation. For a time such a conclusion was held, but it is in the highest degree probable that it is quite unsound.

The *pain* in inflammation is directly dependent upon the altered conditions in the tissues, brought about by the vascular changes. Of these the exudation and migration are the most important, for the pressure in the extra-vascular spaces must thereby be increased whenever the whole of the exuded fluid does not at once drain away. The result is that the delicate nerve fibrils constituting the nerve endings are put upon the stretch. At the same time the increased vascularity and heat must increase locally the conductivity of the nerve, so that afferent impulses which, under normal conditions, would be without effect on sensation, under the abnormal conditions give rise to a sensation of pain. Lastly, pain is probably produced by the action on nerve endings of some of the chemical substances formed locally; but how far this cause co-operates with the others is uncertain.

The impairment of function.—It is not to be expected that the fundamental constituents of a part which is the seat of inflammation should escape without change when the small blood-vessels with which they are in the closest contiguity, and upon which they depend for their nutrition, are modified so profoundly as they are. In many instances, indeed, it is clear that these tissue cells must be affected by the irritant first and to the greatest extent. In the case of the frog's mesentery, the action of the irritant which leads to the changes we have described must modify the endothelial cells covering the mesentery before it can manifest itself upon the vessels. So, too, when the skin is exposed to the action of heat or blistering fluid the epidermal layers must bear the brunt of the irritant before it can bring about changes in the vessels which lie in the corium.

Now, since these essential elements of a part, wherever they may be situated, are the true functioning elements of the part, it follows that when the region in which they are situated is the seat of inflammation, these essential elements must suffer in their power to carry out their functions normally. Whether this impairment of function is of vital importance to the economy or not must depend both upon the nature of the elements themselves, and upon the degree to which they are injured. Thus the hepatic cells may, as in acute yellow atrophy, be

entirely disorganised over large areas, with the result that the hepatic functions are profoundly altered and death occurs. So, too, when inflammation affects the heart the changes induced in the cardiac muscle may be so severe that the heart is no longer able to carry out its functions normally, and death occurs from syncope. But not every hepatic or myocardial inflammation is directly mortal, because it is not in every case that so severe and widespread a set of changes occurs. Nevertheless, whether little or much, whether important for the economy or insignificant, the essential elements of a part which is the seat of inflammation must suffer, and *pari passu* their function must be impaired.

THE CAUSES OF INFLAMMATION

Inflammation does not arise spontaneously ; it is called forth by the action of an irritant. Irritants may be divided into two great classes—organised and unorganised. The greater number of organised irritants are bacterial, and therefore vegetable ; but animal irritants are known, *e.g.* the entozoa, trichina spiralis, chigæ, pediculus capitis, etc. Unorganised irritants are of the most diverse kind—acids, alkalis, wounds, heat, cold, electricity, necrosed portions of the animal's own tissues, wind, excessive muscular exertion, etc. The unorganised irritants all agree in producing the phenomena that have been described above, and theoretically they agree in being *aseptic*, *i.e.* unaccompanied by the presence of living bacterial micro-organisms. Practically, however, the difficulty of obtaining complete asepsis is so great, especially where the skin is affected, that even inflammations primarily caused by unorganised irritants are, *as we see them*, almost invariably complicated by the presence of bacterial irritants and the inflammation which those bacterial irritants induce. One great difference, however, obtains between inflammations caused primarily by one or other of the two classes of irritant ; for the inflammation resulting from the direct action of an unorganised irritant, however extensive, is strictly localised, while, on the contrary, the inflammation resulting from the direct action of an organised irritant shows a tendency to spread. This difference, of course, depends upon the fact that the organised irritants are living and capable of multiplication. When we remember that under favourable circumstances a bacillus (*e.g.* *B. subtilis*) divides into two in about twenty minutes, and that multiplication goes on in geometrical progression at the same rate until some factor intervenes to check the rate of growth, the fact that inflammations of this kind tend to spread, and sometimes to spread with fearful rapidity, becomes quite intelligible. A slight scratch on the finger made during a post-mortem examination may, in rare cases, in the course of forty-eight hours, have led to an intense diffuse inflammation of the entire arm, with perhaps general infection of the body and death.

Pathogenetic bacteria do not always produce inflammation unless the term inflammation is stretched to an unwarrantable degree. Thus the bacillus of tetanus may kill without the appearance at any time of a focus of inflammation, even at the point of entrance of the bacillus into the body. As a general practical rule it may be said that the more powerful the toxins formed by a given variety of micro-organism, the less likely is it to produce a focus of inflammation when inoculated. This brings us to the question of the intensity of irritants.

The intensity of an irritant of either class may vary indefinitely. Thus, heat applied to the skin may be so slight as to cause a mere transient redness with slight increase of lymph-flow through the walls of the dilated vessels; in this case one can hardly speak of inflammation as being present, for the condition is consistent with normal function rather than pathological, the heat rather a stimulus than an irritant. On the other hand, the intensity of the heat may be so great that it kills the tissues on which it acts outright, and here again inflammation is absent, for inflammation can of course only occur in still living parts. But between these two extremes there is a wide range over which heat produces inflammation. A localised redness with some pain will result from a short application of moderate heat; a simple serous blister will result if the heat is greater; and distinct destruction of tissue with severe and widespread inflammation if the heat is very severe. A similar variation in the result will follow if the length of time varies during which heat of a given degree of intensity is allowed to act: a moderate heat acting for a long time producing a severer inflammation than if it acts for a short time, and perhaps as severe an inflammation as an intense heat of short duration.

In the case of bacteria the intensity of the irritant varies as much, and is a matter of the greatest importance. A strain of streptococcus pyogenes may be of so low an order of virulence that when inoculated into the ear of a rabbit it produces only a slight local swelling and redness. Another strain, morphologically and culturally indistinguishable from the first, may kill the animal after leading to gangrene of a greater part of the ear; while yet a third strain, also indistinguishable from the others except by its results, may be so virulent that it kills the animal in a few hours by a general blood infection, and before there has been time for manifestation of more than a very slight local inflammation at the seat of inoculation. So, too, it is well known that epidemics of diphtheria, typhoid fever, influenza, etc., vary greatly in severity and in the degree in which inflammatory phenomena enter into the clinical symptoms. This fact is most probably to be ascribed to variations in intensity of the strains of micro-organisms causing the different epidemics.

Practically it is only few species of bacteria that are of clinical importance, and these are in some cases bacilli, in others micrococci

(whether staphylococci, streptococci, or diplococci), in others spirilla and vibriones, and, in a few, higher moulds. Relatively to the vegetable micro-organisms, animal micro-organisms are so rarely the cause of inflammation that they may be neglected here. In the laboratory, however, a large number of bacteria not usually pathogenetic may, by taking special measures, be shown to induce inflammation; theoretically every species of micro-organism may do so. These measures consist essentially in lowering the vitality, and therefore the resistance, of the animal. In such an artificially-prepared animal, a strain of micro-organism of so low an order of virulence that it fails to produce inflammation when inoculated into a normal animal, may produce as severe an inflammation as an intensely virulent strain would produce in a normal animal. Examples in clinical practice of the fact which the above-mentioned experiment shows are of common occurrence. Thus irritants which are without important effect upon healthy persons may produce very severe results in persons debilitated by disease or excess. A needle-prick, or a small incision in the skin over the front of the leg of a healthy person is a trivial matter, but in a person the subject of Bright's disease the same irritants may initiate an inflammation ending in suppurative cellulitis of the whole member and death. The danger of even slight surgical operations in alcoholic, albuminuric, and diabetic patients is well known.

Since the organised irritants are living and capable of multiplication, the time factor comes in with regard to them as it does with regard to the unorganised irritants; but not altogether in the same way. So far as the inflammation depends upon the action of toxin elaborated by the bacteria, the effect of time is the same for both classes of irritant, for the toxin itself is an unorganised irritant. But one has in addition to remember that time modifies favourably or unfavourably the rate of growth of the micro-organism producing the toxin, and that therefore the element of mass of the prime irritant enters largely into the question. Moreover, the mass of the organised irritant again reacts upon the amount of toxin elaborated, and both of these upon the steps taken by the tissues to antagonise the primary and subordinate irritants. Hence in the case of the organised irritants the time factor becomes not only a highly important, but also a highly complicated, consideration in determining the degree and kind of inflammation that results.

There is great difficulty in deciding whether the nervous system takes an active share in the production of inflammation. It is quite certain that the course which an inflammation runs in a given part varies very considerably, according as the innervation of that part is normal or impaired, and that conditions which are without pathological result upon normal tissues act as severe irritants upon the same tissues if they be deprived of their nervous control. There is no doubt, for example, that mere pressure will lead to the appearance of severe bed-

sores in a person whose spinal cord has been injured, or that in a person suffering from *tabes dorsalis* the sclerosis of the posterior columns of the cord and the impaired sensation of the lower limbs which results therefrom are accountable for the severity of the inflammation which is liable to follow a slight injury to the foot (perforating ulcer). But these are only special exemplifications of the general law that when a tissue is cut off from its nervous supply its nutrition suffers; they do not affect the main question as to whether the nervous system aids in the initiation of inflammation. The evidence we possess on this point is meagre, but it strongly indicates the probability of a nervous control over the occurrence of inflammation. It is chiefly contained in the two following facts: first, new growths, which are unprovided with a nervous supply, do not manifest inflammation; second, true inflammatory phenomena (*e.g.* the formation of a blister) may in suitable persons be induced by hypnotic suggestion alone.

VARIETIES OF INFLAMMATION

The number of varieties into which inflammation has been divided and subdivided are legion. Thus one reads of inflammation as "acute," "chronic," "parenchymatous," "interstitial," "catarrhal," "croupous," "diphtheritic," "suppurative," "erysipelatous," "septic," "spreading," "specific," and so on. These qualifying terms indicate the dominating characteristic in particular cases, and consequently are of some value, but it is of prime importance to recognise that the underlying processes of inflammation are everywhere the same, though the ultimate pictures in two given cases may be widely different. The acute catarrhal inflammation occurring in the naso-pharynx when a person suffers from a "cold in the head" seems at the first glance widely different from an acute peritonitis or an acute inflammation of bone. These acute varieties seem widely different from a chronic tuberculous inflammation of the ankle joint or a chronic pleurisy, and these again from erysipelas or hæmorrhagic smallpox. Nevertheless there is in each of them fundamentally the same dilatation of blood-vessels, with exudation of fluid and migration of leucocytes, accompanied by degenerative changes¹ of the essential tissue elements.

Nor should it be a cause for wonder that inflammation is protean, since it may affect so many different tissues, and be brought about by so many different causes. The catarrhal inflammation shows in the exudation a plentiful supply of mucus and many cells, because the seat

¹ Though degenerative changes are always found in inflammation, it must of course not be supposed that the degenerations and inflammation are always allied. Many instances of retrogressive change might be given (*e.g.* fatty degeneration of the heart, colloid degeneration of carcinomata, vitreous degeneration of muscle), in the occurrence of which inflammation plays no part whatever.

of the inflammation is a mucous membrane, the essential cells of which normally form mucus. When they are supplied with an excessive amount of blood and lymph, and at the same time are the seat of irritation, they proliferate very rapidly, and exercise their function abnormally by breaking down abnormally rapidly and extensively into mucus, and by being themselves bodily cast off. Since they are superficial they readily escape with the mucus they form and the inflammatory exudation poured out into the nasal passages. It is just as reasonable to expect the presence of such characters when a mucous membrane is the seat of inflammation, as to expect their absence when, for example, the tibia is the seat of acute inflammation. And conversely, it is just as reasonable to expect that severe pain, and an absence of obvious redness and swelling, will characterise an acute inflammation of such a tissue as bone where the blood-vessels are small, the tissue resistant and the absorbents few, as it is reasonable to expect relatively little pain, much redness, and much swelling when so vascular and distensible a tissue as the mucous membrane of the naso-pharynx is affected. It is therefore quite unnecessary to discuss the varieties of inflammation at length; with a little thought the salient characters of an inflammation of any particular tissue can be predicted with confidence.

Some of the terms that have been applied to varieties of inflammation are singularly unfortunate. This is notably the case with "parenchymatous" and "interstitial" inflammations. They were introduced to indicate in the first case that the essential elements of the part concerned are the seat of inflammation, but that the supporting structures are free, and in the second case the exact converse. But it is clear, since inflammation is a process invading in its essence the vascular system, and since all blood-vessels run in "interstitial" connective tissue, that every inflammation must by its very nature be interstitial. And it is also clear that it is impossible for the blood-vessels in a part to be affected by inflammation without a coincident interference with the nutrition of the essential elements of that part, so that every inflammation must be parenchymatous. The disadvantages arising from the use of these terms would be less were it not that to the term "interstitial inflammation" a special significance has been given. In the case of such a tissue as the kidney, where the amount of true glandular substance enormously outweighs the amount of interstitial connective tissue, and is of extreme vulnerability, it is clear that any inflammatory condition must show itself chiefly by histological and functional alterations of renal elements. To term an inflammation of this kind "parenchymatous" is unscientific, though perhaps convenient. But in the case of the so-called interstitial inflammations the case is different. We know, especially in the kidney and liver, conditions in which there is a great excess of interstitial connective tissue, much of which is undoubtedly of new formation. Now since it is a fact that chronic inflammatory conditions

are often accompanied by formation of a considerable amount of fibrous or cicatricial tissue, it was (and still is by some authorities) believed that the hepatic and renal fibrotic conditions, to which reference is now being made, represent late stages of an inflammation affecting the interstitial substance of the organs in question. These conditions were therefore termed "chronic interstitial hepatitis" and "chronic interstitial nephritis." A similar morbid process occurs at times in the central nervous system, but here the term *sclerosis* has been applied, and the idea that the adventitious fibrous tissue is "inflammatory" has hardly been raised, and much less that it is "interstitial."

Yet another closely similar condition to the preceding is known in "fibroid degeneration" of the heart, a condition in which irregular foci of fibrous tissue are found to replace portions of the myocardium. Though the view has not been widely held, some authors have regarded the cardiac change as a "chronic myocarditis." In the case of these hepatic, renal, nervous, and myocardial affections it is, however, highly doubtful whether true inflammation has ever played any part whatever. Certainly one never sees specimens of liver, kidney, or spinal cord in which there is a great excess of young fibrous tissue, such as is seen in a mass of young cicatricial tissue; even in the case of myocardial fibrosis, which differs from the others in that it may possibly in some cases be a true sequel of syphilitic inflammation, young fibrous tissue is not met with, but always fully formed and dense fibrous tissue. The matter is a very difficult one to decide, but it is probable, from the evidence given by numerous experiments, that we must consider the adventitious fibrous tissue in the light of a replacement tissue. To take two specific examples. Alcohol is perhaps the chief cause of chronic fibrosis of the liver, and it has been found that when administration of alcohol to animals is followed by fibrosis of the liver the hepatic cells undergo degeneration first, and proliferation of connective tissue cells in the liver only makes its appearance subsequently. So also, if a hemisection of white matter of the cord be made, tracts of degeneration rapidly make their appearance, but are only much later replaced by that newly-formed fibrous tissue derived from the neuroglia which characterises sclerosis. That is to say, the increased formation of fibrous tissue takes place to fill up a potential lacuna occasioned by the death, degeneration, and disintegration of the hepatic cells or nerve fibres.

It is obvious that if these facts indicate the view we have to take of the pathology of the fibroses, they can hardly be termed forms of inflammation. It may of course be that the retrogressive changes in the hepatic and nervous elements cause them to act as a mild irritant—or, rather, a stimulus—to the connective tissue cells in the neighbourhood; and if this be so, the formation of fibrous tissue here is identical with its mode of formation as a sequel to inflammation. But this only means that the connective tissue cells in both cases proliferate in answer to a stimulus, a

fact of which we are already aware, and one which does not in any way affect the main point at issue. Then, too, the changes seen in a definitely chronic inflammation are widely different from those met with in the fibroses. *Chronic inflammation* is by no means an uncommon condition. But however chronic a true inflammation may be, however greatly the newly-formed fibrous tissue may preponderate in it, there is always some point at which the acute changes of inflammation are present. It may be that the irritant is of a very low order of intensity, but highly persistent, with the result that while acute changes are only manifested immediately round the irritant, its prolonged action as a stimulus to proliferation of connective tissue cells leads to an extensive new formation of fibrous tissue in the neighbourhood. It may be that subordinate irritants arise and lead to definite inflammation throughout a newly-formed and therefore highly vulnerable reparative tissue. But whatever the explanation in a given case of chronic inflammation may be, we always find it to be a condition in which acute inflammatory changes are present side by side with well-marked and preponderating reparative changes, *i.e.* few and small foci of migrated leucocytes are present side by side with many and large foci of newly-formed fibrous tissue. Even if we were to concede the point that the fibroses commence as interstitial inflammations, the fully-established conditions are so different from true chronic inflammations that they have no right to be called by the same name. It were as just to term the umbilicus itself, or any other scar, a focus of chronic inflammation.

In the case of certain micro-organisms the characters of the resulting inflammations, and perhaps the seats in which they are commonly found, are relatively so constant that the micro-organisms themselves, and the inflammations they produce, have been termed *specific*. Thus the bacillus of typhoid fever is the specific cause of a specific inflammation affecting the Peyerian patches in the ileum; the bacillus of glanders, of a specific inflammation of the nasal mucous membrane; the diplococcus of gonorrhœa, of a specific inflammation of the urethra; the bacillus of diphtheria, of a specific inflammation of the throat, and so on. All specific inflammations depend upon definite bacterial causes.

THE SEQUELS OF INFLAMMATION

Without attempting to frame a definition of inflammation, we may say that it occurs in a part which has been subjected to the action of an irritant, and is accompanied by vascular changes, exudation of fluid, migration of leucocytes, and degenerative changes in the essential elements of the part affected. It is, however, a condition of unstable equilibrium, and at once passes into one or other of the sequels of inflammation. To these sequels attention must now be turned.

When inflammation has become established in a part two kinds of

results may follow, according to circumstances. On the one hand, if the irritant action ceases, the whole process recedes, the condition of the blood-vessels returning to normal, the exudation draining away, the migrated leucocytes being removed, and the damaged tissue cells being in one or other way repaired. This termination has its exact counterpart in the changes which supervene in a gland or muscle after it has been exercising its function, and may therefore be termed *physiological*. On the other hand, if the action of the irritant continues, the changes occurring in inflammation continue, more and more tissue cells being destroyed, more fluid being exuded, more leucocytes migrating. This termination has no counterpart in physiological life, and hence, besides the physiological, there are also *pathological* sequels of inflammation.

The *physiological sequels of inflammation* are *Resolution* and *Repair*. They invariably go hand in hand. For since as the result of irritant action tissue elements are always affected, it is always necessary that such elements as have been killed should be removed, and that the space left by their removal should be filled up. Concerning resolution nothing in particular need be said here, for the processes in which it consists are the exact converse of those occurring in inflammation. With regard to repair, consideration of the processes in which it consists will be postponed until the pathological sequels of inflammation have been described. For if repair is necessary whenever inflammation has become established, it is even more necessary whenever continuance of irritant action has led to continuance and excess of inflammatory phenomena.

Pathological sequels of inflammation.—It has been said above that the pathological sequels of inflammation occur whenever an irritant continues to act upon a tissue. From this it follows that they are diametrically opposite to resolution and repair, and essentially are brought about by an excess of those changes which together combine to constitute inflammation. They may be invariably referred to one or other or both of the two following categories, viz. (1) suppuration and abscess; (2) gangrene and other forms of necrosis.

Suppuration and abscess-formation consist fundamentally in the production of pus, a faintly alkaline fluid of specific gravity 1030-1033, which separates on standing into a pale yellow opaque deposit, and a supernatant clear straw-coloured fluid (liquor puris), and which commonly becomes "ropy" or viscid on addition of caustic alkali, and does not coagulate spontaneously. In its composition liquor puris approximates very closely to blood plasma, but it differs therefrom in certain points, the most noteworthy of which is that the greater part of its proteid exists in the form of albumoses. It is probably upon the presence of the latter constituent that the absence of auto-coagulability of pus largely depends, for we know by experiment that the natural coagulability of the blood may under certain conditions be completely abolished by

intravenous injection of albumoses. The deposit from pus varies according to whether the pus has been derived from an "acute" or from a "chronic" or "cold" abscess. If from an acute abscess, it consists principally of corpuscles differing from the granular leucocytes of the blood hardly more than in the fact that the nuclei are generally multiple. The cells often show amœboid movements on the warm stage, and bear many granules which, since they are soluble in acetic acid and do not stain black with osuric acid, are evidently not fatty; nevertheless true fatty degeneration of pus cells is of common occurrence. Besides these cells such pus generally contains some fairly large mononuclear cells not bearing granules, and varying numbers of coarsely granular oxyphil ("eosinophil") cells. If the pus is taken from a chronic abscess, the deposit consists for the most part of granular fatty and amorphous débris, and the cells are few in number.

An *abscess* is a localised collection of pus, but special names are often given to abscesses in special situations. Thus a collection of pus in the pleural cavity is termed an empyema; in the pericardial sac, a pyo-pericardium; in the anterior chamber of the eye, a hypopyon; in the fallopian tube, a pyo-salpinx; and furuncles, boils, carbuncles, are terms used for varieties of pus formation in the subcutaneous tissue.

The mode after which an abscess is formed is shortly as follows:—An irritant, *e.g.* a small collection of micro-organisms, becomes fixed at a certain point, and here the micro-organisms multiply and form their specific toxin. The toxin induces degenerative changes in the tissues immediately around, and organisms and toxin lead to inflammation. As a result, exudation of fluid and migration of leucocytes take place, the leucocytes being attracted towards the focus of irritation. These phenomena are pronounced because the irritant action is persistent, and because the tissue elements destroyed by the bacterial toxin themselves act as supplementary irritants and tend to perpetuate the inflammation. Much of the exudation fluid coagulates, and this, together with the increased number of cells in the part, leads to swelling and an increased hardness of the part to touch. As a result of the phagocytic action of the cells, and in some cases of the peptonising action of an enzyme elaborated by the bacteria, the fibrin and dead tissue elements in the neighbourhood of the focus of irritation are dissolved, so that in the centre of the previously firm mass of inflammatory tissue a drop of fluid makes its appearance. In this fluid are suspended numerous leucocytes—living, dying, and dead—together with many of the micro-organisms themselves. Whether it contains in addition cells derived from proliferation of the tissue elements, and in particular newly-formed connective tissue cells, is doubtful. Stricker held that all pus cells are of tissue origin. Cohnheim held just as vigorously that they are all of hæmal origin. Probably the truth lies somewhere between the two views, but undoubtedly nearer that of Cohnheim. In any case this drop of

fluid is the first drop of pus. The whole now constitutes in reality a tiny abscess, though the name is usually reserved for larger accumulations of pus. But whether the quantity of pus is microscopic, or amounts to a pint or more, the pathology of abscess formation is always the same.

Another pathological sequel of inflammation is *ulceration*. An ulcer is formed in exactly the same way as an abscess, and differs from it only in the fact that the ulcer is situated from the first on a surface, whereas an abscess is always situated in the depth of the tissues, though it frequently extends up to and may burst upon a surface. As a result of its superficial position the pus formed on the floor of an ulcer drains away as rapidly as it is formed; nevertheless a thin layer of pus always covers the floor of an ulcer just as pus always lies next to the wall of an abscess.

In the great majority of cases the cause of suppuration, with the accompanying formation of an abscess or an ulcer, is demonstrably bacterial, and certain varieties of micrococci are so frequently met with in connection with suppuration that they have been termed "pyogenetic." The most important pyogenetic cocci are staphylococcus pyogenes aureus and albus, streptococcus pyogenes, micrococcus gonorrhœæ, micrococcus pneumoniae. Theoretically, however, all bacteria may be pyogenetic, and practically bacillus tuberculosis, bacillus pyocyaneus, bacillus typhosus, and actinomyces, are frequently the direct causes of pus formation, though they are not generally included amongst the pyogenetic bacteria. It has been proved experimentally that non-organised irritants *may* be the cause of pus formation, but it is probable that in ordinary life aseptic pus, that is, pus which has been formed without the concurrence of micro-organisms, is never met with. Practically the presence of pus invariably implies the presence of micro-organisms. For some reason that is not thoroughly understood the actual bodies of bacteria, even though dead and artificially freed from admixture with toxins, are far more effective in leading to the formation of pus than the toxins themselves, apart from the bacteria which formed them. Probably this fact depends in some way upon the phenomena of chemiotaxis and phagocytosis, phenomena which appear to be of fundamental importance in the question of suppuration and abscess formation.

The continued effects of an irritant upon the essential elements of a part are also manifested by the occurrence of *gangrene* and *other forms of necrosis*. These effects vary within wide limits according to the intensity of the irritant, the vitality and vulnerability of the tissue affected, and so on. Sometimes (*e.g.* in carbuncle, Peyer's patches in enteric fever, bone) the tissue is so deeply involved that a portion of it dies in mass, constituting a "slough" in the case of soft tissues, a "sequestrum" in the case of bone. Where local death involves a whole member, *e.g.* a toe or foot or a considerable part of the lung, the condition is known as "gangrene." At other times (*e.g.* abscess,

most forms of ulcer, disease of vertebræ, etc.) the dead essential elements of the tissue are thrown off in microscopic masses; this form of local death is commonly seen in the "ulceration" of soft tissues; for the similar condition in bone the term "caries" is reserved. Lastly, soft tissues in which inflammatory processes are going on, especially if they be very severe, may die in mass after they have become soaked in exudation fluid which has subsequently coagulated. To this form of tissue death the term "coagulation necrosis" has been applied; one of the best examples is the "false membrane" formed on the fauces in diphtheria. In all the cases cited, however, the underlying pathological process is one and the same.

Cessation of irritant action.—The pathological sequels of inflammation may be so extensive that they bring about the death of the individual in which they occur, but this is not necessarily the case. After the irritant which has led to them has persisted for a certain length of time, the tissues themselves may gain the upper hand and bring about cessation of irritant action, and allow the physiological sequels of resolution and repair to assert themselves. This result is chiefly brought about by means of (1) dilution of the irritant, (2) removal of the irritant, (3) encapsulation of the irritant. These means are adopted by the body under different circumstances. Thus, the exudation which accompanies inflammation dilutes the irritant if it be a fluid such as a bacterial toxin or a mineral acid; as a rule, the more intense an irritant of this class the greater the amount of exudation, relatively to cells, poured out by the blood-vessels in the inflammation which it occasions. Removal of an irritant may be in part carried out by its excretion by kidneys, intestines, liver, salivary glands, etc. This is true of liquid irritants, like toxins, and also in some measure true of solid irritants, such as bacteria. Nevertheless where the irritant is solid and not completely insoluble, *e.g.* a catgut ligature or the bodies of bacteria, it is generally removed by phagocytosis. If it be practically insoluble or of very large size, *e.g.* a bullet or a large sequestrum, it may become encapsulated by the formation around it of a barrier which first of all consists of coagulated blood fibrin, etc., and afterwards of definite fibrous tissue or bone newly formed by the tissues, in the midst of which the irritant lies. For the occurrence of encapsulation it is further necessary that the irritant should be aseptic, otherwise by its persistence it will lead to abscess formation.

Irritant action is also diminished or arrested by other means, the exact share taken by which in any given case it is impossible to measure. Thus when a joint is inflamed the muscles moving it in health now tend to keep it immobile, and this not only as the result of direct volition, but also automatically. Apparently the continuous painful impulses passing up to the cord induce reflexly a condition approaching to a prolonged tonic contraction of the muscles of the joint. So, too, it is

held by many authorities that the fever which often accompanies inflammation of a part is a means whereby bacteria are killed or weakened and their toxins are destroyed. Though there are many difficulties in the way of regarding fever in the simple light of a "purifying fire," it is certain that in many instances of infective disease the prognosis is better if the patient's temperature rises to a fair degree than if it remains low. Lastly, in the case of bacteria and their toxins, cessation of irritant action is largely or entirely brought about in some cases by the action on them of bactericidal and antitoxic substances present in the blood. Further reference to these substances will not be made, since they have been discussed in the article on the "Infections," but in the case of organised irritants their action is often of the first importance in preparing the way for repair.

Phagocytosis and chemiotaxis.—Phagocytosis is one of the most important methods whereby irritants are removed. The process is practically identical with that whereby an amœba obtains its food. The amœba puts forth pseudopodia, and envelops the particle to be ingested by flowing around it. If the particle be digestible, it is enclosed in a vacuole and digested with the aid of an acid secreted into the vacuole by the amœba; if it be incapable of digestion, it is simply expelled after being held for a longer or shorter time in the body of the animal. The parallel between a leucocyte and an amœba has not yet been established in all its details—notably it is unknown whether an acid is secreted by the leucocyte. But there is no doubt that under certain conditions bacteria and other foreign particles are taken up by leucocytes and in their bodies undergo degenerative changes. We have no reason, however, to believe that phagocytosis is a function devoted to the nutrition of leucocytes; probably it is rather a scavenging function, concerned with the removal of foreign particles of whatever kind from the tissues.

While it is certain that phagocytic cells can exhibit their function towards dead material, such as particles of carmine or carbon, dead bacteria, etc., it was long a matter of discussion whether they can englobe living bacteria. Metchnikoff, who was the first to adapt the phenomena of phagocytosis to modern pathology, and to whom indeed we owe the term "phagocytosis," held that they can do so even when the bacteria are fully virulent. Upon this view he based his theory of immunity from disease, but he was opposed vigorously by German pathologists who maintained that, though phagocytosis can occur in the case of still living bacilli, it is only when they are close to death or at least when their main weapon of offence—the toxin they secrete—has been neutralised by some other means. It is probable that this view is the correct one; at any rate it is certain that phagocytic cells are far less numerous in the neighbourhood of intensely virulent bacteria than they are in cases in which the virulence of the bacteria is less.

Leucocytes are not the only cells to exhibit phagocytosis, for fixed

endothelial cells lining capillaries and lymphatics certainly may be intensely phagocytic, as, for example, in the liver, and it is possible that the same is also true of rapidly proliferating connective tissue cells. Nor are all varieties of leucocyte phagocytic. It is an easily recognisable property of the finely granular oxyphil (multi-nuclear) cells and hyaline cells, but probably never occurs in the case of coarsely granular oxyphil ("eosinophil") cells and lymphocytes. Giant cells in some cases are phagocytic, in others apparently not.

The occurrence of phagocytosis in inflammation is closely bound up with the migration of leucocytes through the vessel walls. At the present time it is generally held that the products of bacterial life-history exert an attractive or a repulsive action upon leucocytes and other wandering phagocytic cells. This action has been termed *chemiotaxis*, since it is most probably of a chemical nature at bottom; and where the leucocytes are attracted to the bacteria chemiotaxis is said to be *positive*; where repulsion occurs it is said to be *negative*. Evidence in favour of a definitely negative chemiotaxis, *i.e.* evidence that actual repulsion of leucocytes occurs, is not nearly so satisfactory as that in favour of the positive variety. Many authors, indeed, while allowing that various poisons may paralyse phagocytes and therefore prevent the occurrence of positive chemiotaxis, hesitate to accept the view that actual repulsion of these cells ever occurs.

Physiological sequels of inflammation—regeneration and repair. When a tissue has been destroyed it is possible that the space which has been left, whether macroscopic or microscopic, may be filled up in two ways: either new tissue elements similar in all respects to those which have been destroyed may be produced—regeneration—or else the space may be filled up by tissue of quite another kind. Except in the case of the epithelial and the connective tissue groups, where it is the rule, strict regeneration of tissue after its destruction is rarely met with, and even in the case of the connective tissue group regeneration of cartilage never occurs, while bone may be repaired by the new formation not of bone but of ordinary fibrous tissue. So far as muscle is concerned, regeneration of the striated variety never occurs, and regeneration of unstriated muscle only in the case of the muscular coats of those new arterioles and venules which are concerned with the nutrition of the young reparative tissue and are formed from pre-existing vessels in the periphery of the focus of inflammation. In the case of more complex forms of gland tissue, such as kidney and liver, it is doubtful whether repair ever occurs by true regeneration of the composite elements composing the gland, but in the light of recent researches it is impossible to say that true regeneration never happens. If it occurs as a sequel to inflammation it must be uncommon and inconsiderable, for when a portion of kidney, liver, or mammary gland has been removed the space is filled up by fibrous tissue and not by

newly-formed gland substance. With regard to nervous tissue we are certain that nerve cells once destroyed are never reproduced, but in nerves themselves a return of function after injury is known. Here perhaps we have a true case of regeneration in that the axis cylinders which have been destroyed are replaced by new axis cylinders developed by growth of those portions of the original axis cylinders still connected with the nerve cells in the anterior horns of spinal gray matter, or in the posterior root ganglia, as the case may be. Such a condition after injury to a nerve is, however, by no means invariable; the anatomical continuity after complete severance may be restored, but by ordinary fibrous tissue and not by conducting nervous elements.

In the vast majority of cases repair consists in replacement of the dead and disorganised tissues by an increased growth of fibrous tissue. This may be so small in amount as to be invisible or may be sufficiently great to constitute a cicatrix or scar. Thus in a wound involving the true skin, whether it goes no deeper than the corium or involves the subjacent muscle, after the effects of irritation have ceased, the breach is entirely filled up by fibrous tissue itself covered in by epithelium regenerated from the uninjured epithelium around the wound, but carrying neither sweat glands, hairs, nor sebaceous glands. Where the breach of continuity involves bone, repair of the bone itself is generally carried out by a new formation of bone. But this only depends on the fact that the stimulus to increased growth and the increased amount of nutriment are brought to bear on the specialised connective tissue constituting the periosteum, the essential cells of which have the peculiar property that they form around them an inter-cellular substance which becomes impregnated with calcium salts, whereas fibrous tissue cells form around them an inter-cellular substance in which calcium salts are, usually, not deposited. Nevertheless, even in the case of bone, where conditions are unfavourable, a fracture may be bridged over, not by bone, but, as has already been said, by dense fibrous tissue.

The new formation of fibrous tissue certainly depends upon a proliferation of the fixed connective tissue cells in the neighbourhood of the focus of inflammation, to supply the nutriment necessary for which new capillaries are formed from pre-existing capillaries. This new tissue consisting of young and highly cellular fibrous tissue with its new blood-vessels—granulation tissue—is at first highly vascular, and for that reason a young scar is redder in colour than the skin around. But later, owing to the inherent property of fibrous tissue to contract, the greater number of these new vessels become obstructed and disappear, causing an old scar to present its characteristic depressed dead-white appearance. Whether migrated “hyaline cells” of the blood take a share in the new formation of fibrous tissue it is impossible to say with certainty, since they are indistinguishable, when in the tissues, by any methods at our disposal, from young rapidly proliferating con-

nective tissue cells. But it is probable that they are really of connective tissue origin and are hæmal, so to speak, accidentally. If that be so, when they migrate they do but return to their original home, and it would not be extraordinary if they resumed their original function of forming connective tissue. With regard to the other varieties of leucocyte, it is now generally agreed that they do not take a share in the formation of new fibrous tissue, though this question formed at one time perhaps the fiercest of the many fierce controversies that have raged around the subject of inflammation.

THE SIGNIFICANCE OF INFLAMMATION

As in the case of fever, so with inflammation, opinions have constantly varied as to whether the process is deleterious or beneficial to the economy. These differences of view have chiefly depended upon different conceptions as to the phenomena which should be included under the term inflammation. By some authors it is held that reparative processes constitute an essential part of inflammation, by others that they are to be sharply distinguished therefrom. With regard to this question it is certainly common to see in a microscopical section showing inflammation a number of fibroblasts with newly-formed fibrous tissue and blood-vessels. But if we consider that this new formation of cells and tissue is definitely dependent upon proliferation and growth of cells, it is clear that repair cannot be a part of inflammation itself. For inflammation is a series of changes brought about by the action of an irritant, and an irritant—as distinguished from a stimulus—always leads to degeneration and not to proliferation. Degeneration and proliferation may be in progress close to one another, for an irritant at one point may be a stimulus at another a short distance away, and therefore inflammation and repair may proceed side by side, as we know they often do. But it is clearly impossible that both processes can be going on at the same time in the same cell. Hence follows the conclusion that before repair can take place at a given point irritant action must cease there: a conclusion of the utmost practical importance. Then, too, some authors include the degenerative processes under inflammation, and therefore regard inflammation as deleterious. But inflammation only occurs in living tissues, and if the dead, dying, and disorganised tissue elements resulting from irritant action are to be classed under inflammation, a slough or an eschar is inflamed tissue. This is certainly not the case, and therefore we have to separate from our conception of inflammation (when considering the significance of the process) all degenerative changes. Degenerative changes are causes and results of inflammation and are therefore present wherever there is inflammation, but the inflammatory process is distinct therefrom.

If, then, the reparative and the degenerative changes must be set on

one side, we are left with the vascular phenomena, viz. with exudation of fluid and migration of cells. Concerning the significance of these we can form some conception. In physiological life the blood plasma is primarily nutritive, secondarily diluent, antitoxic, etc., and there is no good reason for considering that in inflammation these functions are abrogated, especially as there is manifest necessity for an excessive supply of nutriment to the cells whose vitality has been lowered, and for a diluent to destroy and carry away the irritant and lessen its local effects. With regard to the cells we know definitely that in most instances they are phagocytic. Hence we may feel sure that provision of an increased amount of food to injured cells and antagonism to the irritant are two of the most important underlying principles of inflammation. In other words, we must regard inflammation as a beneficial process which clears the way for repair after an irritant has produced degenerative, or even destructive, changes in a vascular part. But it must not be supposed that inflammation is invariably a beneficial process in practice whatever it may be theoretically. For example the exudation poured out in the course of peritonitis is under certain circumstances a very favourable culture medium for bacteria, and if these gain access to the abdominal cavity the final result of what was originally a beneficial process will be intensely injurious. So, too, exudation fluid may accumulate in the pericardial sac, owing to pericarditis, to so great an extent that it seriously interferes with the working of the heart. And, as has already been said, the pathological sequels of inflammation are but results of persistent irritant action, and are therefore manifestations of the evil effects of prolonged inflammation. Other examples might easily be given. The *motive* of inflammation is the benefit of the economy, but benefit to the economy is not always the *result*.

PRINCIPLES OF TREATMENT IN INFLAMMATION

Treatment in inflammation must be local and general, and circumstances must decide in each case which of the two kinds of treatment should receive the greater attention. With regard to local treatment two points stand forth with great clearness. First, irritant action must be reduced to a minimum; second, the tissue elements in the inflamed part must, as far as possible, be given physiological rest.

As examples of the way in which these principles are applied the following instances may be cited. When a joint is inflamed, as in acute rheumatism, the limb is kept at rest until the inflammation has subsided, and at the same time salicylic acid and alkalies, which have been found to exert an antagonistic action on the rheumatic virus, are given internally. When a kidney is inflamed, physiological rest is given by reducing the nitrogenous ingesta as far as possible, and removal of the irritant is promoted by cautiously flushing the kidney with

bland fluids given by the mouth. Rest to the kidney may also be given by promoting the vicarious activity of the skin. This can be attained by sending patients with chronic renal disease to warm and dry climates, *e.g.* Egypt, while in acute cases pilocarpin and hot-air baths are of use. Conversely cold and damp climates and sudden variations in temperature are avoided. When the pericardium is inflamed, bringing with it an inflammation of the myocardium, physiological rest is given to the heart by removing all unnecessary causes of cardiac action, such as muscular exertion, excitement, etc., the patient being put to bed and kept perfectly quiet. If exudation accumulates to such an extent that it becomes a definite obstacle to the heart, it is removed by paracentesis. At the same time, for reasons which cannot properly be explained, application of blisters or of leeches over the præcordial area are often useful. A belladonna plaster, too, applied over the heart area often gives relief, primarily, by easing the pain, and, secondarily, by abolishing that increase of cardiac activity which depends upon the mental excitement due to the pain: perhaps also by some direct sedative action of the absorbed drug upon the heart muscle. When the mucous membrane of the stomach is acutely inflamed, rest is given by restricting the ingesta to small quantities of cold, bland, and unirritating liquid food, or perhaps by interdicting food by the mouth altogether. In some cases the stomach is washed out to remove the irritant; where the gastritis depends upon an extra large meal after a prolonged fast, administration of an emetic, upon the same principle, is often the most effective of all treatment.

As local measures often adopted with marked advantage are local application of heat and cold in the form of poultices, fomentations, cold-water compresses, ice-bags, etc. Probably these agents act by modifying the blood-flow through the inflamed part, but there are many curious and as yet unexplained points with regard to them. To mention only one: in the case of a joint acutely inflamed as the result of a sprain, local application of cold is of the greatest benefit, but if the joint be acutely inflamed in the course of rheumatic fever or gout, application of cold is distinctly injurious.

At the same time as local measures are adopted general principles of treatment must be carried out. However local an inflammation may appear to be it is invariably either the direct cause, or one manifestation of a general disturbance of the body's equilibrium. Hence the patient's strength must be maintained by nutritious and easily assimilated foods and perhaps by the administration of alcohol. When the local inflammation is really but a part of a general disease (*e.g.* the intestinal inflammation in enteric fever, carbuncle in diabetes mellitus) such general supporting treatment is of the highest importance

MALIGNANT DISEASE

The terms "malignant" and "malignancy" bequeathed to us from the days when particularly virulent disease was regarded as being due to the influence of malign spirits, are to be regarded at the present time as conveniently expressing certain general clinical features rather than denoting any special malady and still less any special structural characters. Thus extremely severe and rapidly fatal cases of small-pox, scarlet fever, etc., are sometimes spoken of as malignant. Conventionally, however, these words have come to acquire a somewhat restricted application in respect to some forms of new growth, and since such growths are of frequent and widespread occurrence, it is desirable to give some general account of them that shall be common to any situation in which they may occur.

For the most part "malignant growths" are characterised by the following features:—(a) An advancing infiltration of the tissue in which they occur, which is associated with the absence of any limiting capsule, and a consequent liability to recur owing to the difficulty of complete removal; (b) a marked tendency to form secondary growths, "metastases," built upon an identical type, in the neighbouring lymphatic glands and in the distant organs, caused by the conveyance of particles of the primary neoplasm in the blood, or lymph streams, which act as fresh foci of development; (c) a rapidity of growth, determined in great measure in proportion to the preponderance of cellular elements in the tumour; (d) more or less well-marked clinical characters in part due to the mere intrusion among the tissues of a mass of new material leading to results of a mechanical character, such as increase in size and displacement of organs, pressure effects, etc., but more particularly to the widespread deterioration of health beyond what the local lesion may be held accountable for; this state of cachexia (or acquired morbid constitution) tends to increase, and sooner rather than later leads to a fatal termination. Although these may be regarded as the criteria of malignancy, they cannot be considered as absolute, and exceptions may be made to each one of them; still, for clinical purposes, they form a very generally distinctive group of characters. It may be further observed that these characteristics vary much in the degree to which they are manifested among growths that are included as malignant, such differences being in part associated with the several structural features presented by them, with the situation in which they occur, and with other circumstances peculiar to the individual, and as yet incapable of exact definition. Very rarely do tumours of a simple character take on the character of malignancy, and even then they retain the structural type to which they originally belong.

Anatomical characters of malignant growths.—New growths which manifest malignant characters are found histologically to present two main types of structure.

(i.) *The connective-tissue type or sarcomata.*—The connective tissues which are developed from the mesoblast present normally a wide range of structure in their fully differentiated condition, such as loose and dense connective tissue, fibro-cartilage, cartilage, and bone. Each of these in its earliest stage consists of an “embryonic tissue” (represented in the process of repair from injury or inflammation by “granulation tissue”), composed of hyaline cells, fibroblasts, and a variable amount of fibrous material, distributed in which are capillary blood-vessels. And as such a material may indifferently become developed into any one of the above-mentioned adult structures, so may the sarcomata which are essentially formed of this tissue present bone, cartilage, or fibrous tissue in their composition. Fundamentally consisting of cells, and an intercellular stroma in which are blood-vessels, great variety exists in the character and relative proportion of these several constituents. Thus the cells may be round or spindle-shaped, and of large or small size, or irregular, multinucleated, and of considerable dimensions, the so-called myeloid cells; and such variations determine the name of the growth, *i.e.* “round-celled,” “spindle-celled,” and “myeloid” sarcoma. The stroma may be almost homogeneous in appearance, or exhibit all degree of fibrillation, or it may be cartilaginous or bony, determining the varieties known as myxo-sarcoma, fibro-sarcoma, chondro-sarcoma, and osteo-sarcoma. As a rule the more active and more malignant are those in which the proportion of cells to stroma is greatest, but among the most malignant are those in which the cells have become the seat of a deposit of black pigment—melanin. For though the melanotic sarcomata spread but slightly from their point of origin, they tend to become extensively disseminated, and are especially characterised thereby. It is also noticeable that the urine in such cases usually contains melanin or its chromogen.

Although the sarcomata are very liable to spread and infiltrate adjacent structures, they exhibit less tendency on the whole to involve the lymphatic glands except in the case of the testis or tonsil; although a variety of sarcomatous new growth—lympho-sarcoma—specially affects the lymphatic glands and other adenoid tissue. Secondary growths are most commonly found in the lungs and are spread *viâ* the blood-stream rather than by the lymphatic channels, which are generally absent from sarcomata. Owing to the wide range of differentiation which the component tissue is capable of, the secondary growths are not always identical in structure with the original tumour, but they invariably belong to the same or to a lower type of the connective-tissue series. The subcutaneous tissue, periosteum, medulla of bones, lymphatic glands, and fibrous tissue generally are the commonest sites for the sarcomata.

(ii.) *The epithelial type or carcinomata.*—Malignant growths of this type, known also as true cancers, originate in epithelium whether “squamous,” “columnar,” “spheroidal or glandular.” Genetically, therefore, they are either epiblastic or hypoblastic. Their essential structural characteristic is that they consist of masses of epithelioid cells enclosed in communicating alveoli formed by connective tissue, in which run the blood-vessels and lymphatics, with no intercellular stroma, as is found in the sarcomata.

The cells, which are large, are extremely variable in shape, owing in great part to the pressure to which they are mutually subject; hence round, oval, pyriform, and polygonal forms are met with. The nuclei are usually very distinct, often double, and contain easily seen nucleoli. There are frequently to be found in, and also lying among, the cells towards the margin of the primary growth and in recent secondary formations, one, two, or even clusters of round or oval nucleated distinct objects known as “cancer bodies,” the exact significance of which is still uncertain. By some they are regarded as parasitic organisms, and reference will be made to them later. The cells exhibit several well-marked differences in their modes of disposition within the alveoli, thus they may be packed in dense masses without any appearance of arrangement, except that resulting from mutual pressure. Such is the common plan in most glandular carcinomata, whilst in the squamous epitheliomata, which chiefly develop at the junction of skin and mucous membranes—as at the lips and anus—the cells are grouped more or less concentrically in rounded masses forming “nests,” or they may constitute solid cylinders extending down into the subjacent tissue. In the so-called columnar epitheliomata, which arise in the stomach, intestines, including rectum, and the arteries, the cells are arranged in the form of a tubular gland, the columnar-shaped cells being disposed round a distinct lumen. The amount of stroma is very variable, being reduced to extremely fine strands in the softer (encephaloid) forms, but forming the greater part of the tumour in the denser, harder, and less malignant varieties such as scirrhus; all intermediate degrees being met with. Much difference of opinion has existed as to the real origin and significance of the stroma; whether it is an essential part of the new growth or merely an inflammatory proliferation of the surrounding connective tissue induced by the irritation of the neoplasm. The latter view in the case of the carcinomata appears to be more probable.

(iii.) Intervening as it were between these two chief types of malignant growth are those known as *endotheliomata*, which develop from the endothelia of serous membranes and blood-vessels, and as such are like the sarcomata in being of mesoblastic origin. In structure, however, they conform to the carcinomata, consisting of masses of large cells enclosed in alveoli of fibrous tissue.

These various forms of growth are all liable to undergo changes

chiefly of a degenerative character, and this is especially so in the carcinomata when the cells in the centre of the masses are furthest removed from the blood-supply. Hence it is also that such tumours break down, are prone to ulceration and necrosis, often forming extensive sloughs, and give rise to considerable hæmorrhage. The very vascular and soft sarcomata are also likely to bleed into their substance from rupture of the ill-supported vessels. The greater the amount of stroma and the fewer the cell elements the less likely, as a rule, are these changes to occur. Besides the more common fatty degeneration, the cells of carcinomata may undergo a colloid change which may involve the whole tumour, or only be seen in limited areas. Carcinomata, connected with the abdominal viscera, exhibit this condition most frequently and to the greatest extent, but it is not confined to growths in this region. The alveoli are much distended with a glairy homogeneous fluid in which almost all traces of the cells are lost. Such tumours frequently attain enormous size. Hitherto nerves have not been found as constituents of these various neoplasms. A consideration of these structural characters of malignant growths shows that they are histologically separated by no sharp line from tumours which exhibit none of the features of malignancy, nor from those which are anatomically indistinguishable from the normal tissues of the body, for the sarcomata pass by insensible gradations into fibromata, and columnar epitheliomata closely resemble certain adenomata which differ from normal gland tissue in functional disability rather than in structural peculiarity. At the same time, though there is nothing distinctive in the component elements of a carcinoma, this arrangement of masses of cells in alveoli, which subserve no useful purpose, conforms to nothing normally met with in either embryonic or adult tissues (heteroplasia).

The primary growths are usually but not invariably single, and their secondary offshoots are to be sought chiefly in the organs in direct vascular or lymphatic connection therewith, hence the liver is a common site for secondary deposits from the viscera drained by the portal system, as the lungs more frequently afford a nidus for the development of those particles from a primary growth that escape into the systemic circulation. The extent to which metastatic deposits arise largely depends on the freedom of the communication of the primary growth with the blood-vessels or lymphatics, and upon the proportion of cell elements in the growth; for these reasons the carcinomata are more liable to dissemination by the lymphatics at first rather than by the blood-vessels, being somewhat different to the sarcomata in this respect. There appears to be no doubt that the actual metastasis is affected by one or more still active cells detached from the initial tumour, from which the secondary growths are formed, thus differing in some measure from the secondary infections of tubercle, where the new material is derived from the tissue of the part in which the transmitted bacilli are lodged.

Origin of malignant growths.—Many and varied are the theories that have been held as to the intimate nature and origin of these tumours, and even now the question is far from settled. Nor can it be said that more is known as to the conditions determining the formation of those growths which structurally conform to the tissue in which they appear, and that clinically are known as “benign” or “innocent,” such as lipomata, fibromata, osteomata, etc. Setting aside the view formerly held that the tissue of the part, under certain unknown circumstances, reverted to an indifferent embryonic form from which the new growth of whatever type developed, it may be said that the prevailing opinion favours one or other, or even both of the following hypotheses.

(a) According to the view maintained by Cohnheim,¹ a new growth appearing in an organ owes its origin to some persistent remnant of embryonic tissue, which, retaining its developmental potentiality, has remained latent amid the growth and differentiation of the surrounding material, and subsequently itself taking on a formative activity as the result of some stimulus, gives rise to the tumour, the normal resistance on the part of the surrounding tissues being at the same time diminished. That this is the explanation of certain neoplasms is undoubted, the enchondromata that may form in the parotid gland, and elsewhere, as well as various adenomata and sarcomata, may be distinctly traced to fœtal remains that have for some time remained in abeyance. But such a source is difficult to accept for many new growths, and more particularly for the carcinomata.

(b) The other theory advocated by Virchow regards the new growth as the response of the affected tissue to some perversion of its environment, some irritation. In its crudest form this is represented by a gross injury which so affects the nutritive course of the tissue, as to arrest its maintenance in a state of normal integrity, and determine some reversion, with or without a subsequent modified evolution, which results in the formation of a tissue differing in greater or less degree from that in which it develops. Such a view would approximate new growths in some measure to the new-formed tissue that results from inflammation, and between the two it is often impossible to draw the line. That many new growths do follow on injury and chronic irritation is undoubted, but it is probable that trauma acts rather by rendering the tissues more vulnerable, and by inducing an increased blood-flow as part of the resulting inflammation, than that it is an actual determining cause, at least of malignant growths.

Recent investigations have suggested a more specific nature for the irritant, and there are not wanting reasons for supposing that this may be of the nature of a living organism, and that malignant growths

¹ The theory of embryonic rests had been previously suggested by Virchow, and even earlier (1874) by Professor Durante of Rome.

are the structural expression of an infection, to that extent resembling (as indeed they do in certain clinical features), the infective granulomata, tuberculosis, leprosy, actinomycosis, and syphilis. It may at once be said that nothing approaching proof of such a hypothesis exists at present, and all attempts to propagate the disease in animals by inoculation of portions of growth from the human subject have hitherto completely failed. Although considerable success in this direction has followed when the procedure has been carried out in animals of the same species, such as cats and dogs, nevertheless there are certain indications that some such explanation may prove to be the true one. Numerous examples might be quoted of the accidental auto-inoculation of a healthy surface either by contact with a malignant growth or by a contaminated instrument in the course of operation. Mention has already been made of the presence in the cells of carcinomata of so-called "cancer bodies" and of their probably parasitic nature. Some of the appearances formerly included within this term were clearly due to degeneration and other changes in the cells, but improved means of investigation have demonstrated with almost certainty that many of these bodies are invading organisms. At first regarded as belonging to the protozoa, and placed as gregarinidæ, coccidia, or psorosperms in the class of Sporozoa (see pp. 1, 2, 4), they are now with some reason considered as belonging to the fungi in the group of Blastomycetes. Members of this group of micro-organisms have been cultivated from human carcinomata, and others have been found to be pathogenetic when introduced into animals; one species, the *Saccharomyces neoformans* (p. 3), when inoculated in dogs giving rise to an epithelial growth with malignant characters.¹ If it should prove to be the case that malignant growths are of microbic origin, it would appear probable that the several forms of neoplasm are dependent on different though allied organisms, just as tubercle, syphilis, etc. It is not contended that this parasitic explanation of the origin of cancer is free from objection, for even granting the presence of a micro-organism, it is at least remarkable that the result is restricted to an indefinite proliferation of epithelial cells quite unlike the effect on the tissues following bacterial invasion, where connective tissue as well as epithelial are involved in changes of an inflammatory character.

The responsibility of the tissues in which a new growth occurs for the development of the same is often overlooked; and whether we regard the essential cause as a parasite *ab extra*, or an actively growing embryonal remnant, the receptivity of the tissues and their behaviour has to be reckoned with. Some there are indeed, as Ribert, who would

¹ For an account of Sanfelice's experiments on this subject see *The Parasite of Cancer*, by Dr. W. Russell, *Lancet*, April 1899. *The Infectivity of Malignant Growths*, by Drs. Bellingham Smith and Washbourn, *Ed. Med. Jl.* Jan. 1890—both with numerous references.

wholly attribute neoplasms to a proliferation, normal or perverted, of the tissues, induced by some change in the mutual relationship—tissue tension—of the surrounding parts.

Etiology.—*Sex.*—The exceeding frequency of malignant disease of the mammæ and uterus renders the total incidence of cancer far greater in females; but in respect to other organs males are more commonly affected.

Age.—No age can be said to be exempt from the manifestation of malignant disease. It has been met with in the infant and the centenarian; in the former case the growth is almost if not always of the sarcomatous type, and it is doubtful if true cancer has been seen before the age of 11 years. It is singular that the rectum is the usual site of carcinoma in early life. Mammary cancer is very rare before the age of 25, and uterine cancer previous to 20. "While the forces of growth, development, and reproduction are in greatest activity—during the periods of intra-uterine life, infancy, childhood, adolescence, and adult age—the tendency to cancer is exceedingly small. In both sexes the disease begins to be frequent as soon as the period of perfection has been attained, *i.e.* after the 35th year; during middle age and decline of life the liability to it increases, until about the 65th year; after which period it becomes markedly less frequent, and increasingly so as age advances. The principles that govern the age distribution of cancer in general apply also to its various local manifestations in both sexes."¹

Locality.—Cancer in some form or other has been met with in all quarters of the globe, but it appears to be distinctly less frequent in both tropical and arctic regions, and it may also be said to be rare among the black races.

According to Mr. Haviland, who has made a special study of the geographical distribution of disease, "the cancer fields in England and Wales are found in the sheltered and low-lying vales, traversed by fully formed and seasonably flooded rivers, and composed of the more recently argillaceous formations; and that the districts having the lowest death rates from this cause occupy the more elevated areas composed of the oldest rocks, amongst which the limestone areas are co-incident with the very lowest mortality."² Exceptions, however, can be made to at least the first part of this statement. Many examples could be adduced, showing apparently a prevalence of cancer in very restricted areas and even in houses, numerous individuals, relatives and others resident in the same place being successively attacked, a cir-

¹ Article "Cancer," by F. Roger Williams, F.R.C.S., *Twentieth Century Practice of Medicine*, vol. xvii., to which reference may be made for various statistics connected with the subject.

² Article "Medical Geography of Great Britain," by A. Haviland, M.R.C.S., Professor Allbutt's *System of Medicine*, vol. i.

cumstance which has been quoted in favour of the infective nature of the disease.

Heredity.—That cancer tends to appear in several members of a family in the same or successive generations is common knowledge, and is fully confirmed by scientific observation in numerous cases, even to the extent of three and four generations ; sufficiently often, that is, to exclude mere coincidence. With preponderant frequency also does the growth involve the same organ or region in the same group of individuals. It cannot be held at the present day that it is the disease which is transmitted, rather is it a tendency thereto by which the intrinsic vitality of the cells is so modified as to render them more susceptible to those external influences which actually determine the malignant growth. So far as embryonic remnants give rise to such tumours, the condition is clearly a transmitted one.

Although cancer and active tubercle are seldom met with in the same individual, obsolete tubercle is frequently found, and a large proportion of the cancerous patient's relatives are tuberculous (Roger Williams, *loc. cit.*).

The significance of these several conditions as factors in the production of malignant disease will be largely conditioned by the view taken as to the intimate nature and immediate origin of such growths. Consistent with the infective hypothesis, their influence would be regarded as favouring the susceptibility of the tissues to microbic invasion. Should the assumed pathogenetic organism require, as apparently is the case with such as the malaria parasite, that a stage of its development be passed external to the body, some explanation may be found therein for the supposed prevalence in certain localities, and the same would also help to account for the difficulties hitherto experienced in cultivating the cancer germ.

Clinical characters.—One striking feature of malignant tumours, as indeed of new growths generally, is so, to say, the independence of their existence. Occurring as the former do at and after middle life, the activity of their growth is often in striking contrast to the wasting and deterioration of the rest of the tissues. The demand that they make on the body nutriment may contribute to this condition, but apart from that their vitality is displayed in a manner irrespective of other parts, except that the limits and rapidity of their increase are largely conditioned by the extent of their vascular supply. This independence is further shown by the large proportion of glycogen found in such growths, much exceeding what other organs yield except in early foetal life. But apart from this great formative activity the growth is otherwise functionless, it contributes nothing to the well-being of the body, but on the contrary is in all respects detrimental.

It is certainly the case that the subjects of malignant disease are more frequently those who have enjoyed previous good health and have

led regular lives, and who have been subject to no privations ; indeed it is claimed that it is more prevalent and increasingly so among the well-to-do, being especially connected with the change in a large proportion of the population from agricultural life to residence in towns and industrial occupation ; with it is further alleged a dietary richer in quality and containing more meat.

However this may be, the disease when established tends to determine a grave failure in health progressively advancing to death. This is partly due to the interference with the functional activity of important organs, as stomach, liver, etc., from the destruction of their tissue by the invading growth ; or the ill effect may be in a measure mechanical as the displacement of viscera, or an obstruction to the lumen of canals as the œsophagus or intestine. Or again the hæmorrhage, often repeated and continuous, which follows from ulceration of the growth, may very seriously affect the health and even be responsible for the fatal result. Beyond such obvious causes as these, however, there is frequently developed a cachexia which is intensified should either of the foregoing conditions exist, but which may nevertheless develop quite independently of any, and apparently owes its existence to some direct prejudicial influence excited by the growth itself. What this may be is unknown, but it is surmised that it is of the nature of an autogenetic toxæmia due to perverted metabolic changes which the growth of the tumour has set up. This is quite distinct from the septic effect which may follow suppuration and sloughing in the new formation.

The characteristic features of the cachexia are closely associated with the changes in the blood ; a progressive anæmia being established, marked by a decrease in the number of red blood corpuscles, which exhibit considerable alteration in shape and diminution in amount of hæmoglobin ; a leucocytosis also frequently occurs. From this follow the peculiar earthy pallor and the liability to peripheral œdema, and even serous effusions as well as thrombosis of vessels. The degree of emaciation is variable, but is particularly well marked if the alimentary viscera are involved. The incidence of pain is very uncertain ; many malignant growths undoubtedly run most of their course and give rise to none, but in proportion as the skin, mucous or serous membranes are involved, so generally will be the degree of suffering. Once established it is likely to persist, and is often of agonising severity.

The physical signs and local symptoms will of necessity depend upon the situation of the tumour and on the organs affected.

In a large proportion of cases death is attributable to inanition and asthenia ; sometimes, however, the patient passes into a condition closely resembling the typhoid state (p. 89).

The most satisfactory method of **treatment** is careful and complete removal of the growth and tissues involved ; their destruction by escharotics, calcium carbide, electrolysis, ligature of the supplying

arteries, injections into the substance of the growth of carbolic acid, alcohol, etc., as well as many other plans, have been advocated from time to time, but on insufficient grounds. It is claimed that some success has followed the subcutaneous injection of a mixture of the unfiltered toxins of the streptococcus of erysipelas and bacillus prodigiosus (Coley's fluid) in cases of sarcoma, causing breaking down and sloughing of the tumour, or simple absorption of the same. This treatment is not without risk, as the toxins should be prepared from highly virulent cultures of the streptococcus; the dose should not exceed one-fourth to one-half minim with sterilised water, and may need daily repetition for several weeks.

W. H. ALLCHIN.

GENERAL PHYSIOLOGY AND PATHOLOGY OF
DUCTLESS GLANDS

The activity of glands normally produces either a secretion or an excretion, and secretory activity is further divisible into external secretions and internal secretions.

A secretory gland may not only have an external secretion but may also have an internal, and glands which excrete may also have an internal secretion. The fundamental distinction between an external secretion and an excretion lies in the fact that in the latter the products of the activity of the glands are simply removed from the blood-stream, as for instance in the excretion of urea by the kidney. An external secretion, on the other hand, is characterised by the elaboration by the gland cells from the blood of the substances characteristic of that secretion, as for example the formation of pepsin by the gastric glands or of trypsin by the pancreas. Some glands, such as the salivary, have only an external secretion, others, like the thyroid, have only an internal secretion, others, like the pancreas and the liver, have an external and an internal secretion; some physiologists think that even the kidney, which is perhaps the most highly specialised excretory gland, has in addition an internal secretion, but the evidence on this point at present is not conclusive.

It is possible that, in addition to their secretory and excretory activity, glands have some further and remote action on other tissues of the body, but more especially on the higher functions of the nervous system. It is well known that the removal of certain glands, as for instance the ovaries or the testes, is liable to be followed by disturbance of the function of the higher cerebral centres; in other words, that various forms of mental derangement are liable to occur after such operations, and although it is possible that these effects, like those produced on the general nutrition of the body, are dependent on the effects of an internal secretion, it is also possible that they are brought about by some other and more obscure mechanism.

Many external secretions are known to be under the direct control of the nervous system, as in the case of the salivary glands; others, as for instance the gastric and pancreatic secretions, are probably under such control, although the evidence at present is not conclusive. Some so-called excretions, as that of the sweat, have a nervous mechanism as delicate and complicated as that controlling the secretion of saliva. In others, like the urinary, although it is possible that such a mechanism exists, the only nervous governance known is that influencing the renal circulation and so indirectly the excretion. As regards internal

secretions there is at present no evidence, however probable on *a priori* grounds, that they are under the direct control of the nervous system.

An internal secretion may be defined as an elaboration by a gland of some substance or substances necessary for the healthy metabolism of tissues or organs of the body and reaching these through the blood or lymph stream. The most definite instance of an internal secretion is undoubtedly the formation of glycogen by the liver. The glycogen is gradually and continuously elaborated by the activity of the liver cells and is suddenly, and probably intermittently, converted into sugar and carried away to the body at large as the needs of the economy demand. In this respect there is a close analogy between the phenomena of an internal and of an external secretion, since in such an external secretion as that of the gastric juice there is a gradual and continuous elaboration of pepsinogen and a sudden and intermittent conversion of it into pepsin. The only difference in the two cases being that the one substance, dextrose, is passed into the blood-stream and carried to the tissues, whereas pepsin is passed to what is practically the exterior of the body, namely, the alimentary canal.

Internal secretions of ductless glands.—The thyroid and the suprarenal are the ductless glands in which the evidence of the existence of internal secretions is most definite. In the case of the thymus and the pituitary body, probable as such an activity may be, it is not yet so definitely established. The *thyroid* body consists of a stroma of connective tissue containing the blood-vessels and lymphatics, and embedded in it a number of closed alveoli lined by cubical cells and containing colloid material. This colloid is a complex proteid substance which contains a considerable amount of iodine and some phosphorus; it can be broken up in a variety of ways into a proteid moiety containing a small percentage of iodine, and a non-proteid moiety containing a large percentage of iodine to which the name of thyro-iodin has been given. The colloid substance of the thyroid and both the substances into which it can be broken up possess the active properties of what is described as thyroid extract, but the thyro-iodin is by far the more active. In the light of modern researches the colloid substance of the thyroid can no longer be looked upon as an excretion, but must be regarded as the active constituent of the internal secretion of this gland; in other words, the colloid of the thyroid bears the same relation to the thyroid that the hepatic glycogen does to the liver, the only difference being that whereas the glycogen is removed from the liver through the hepatic veins in the form of dextrose, it is probable that the colloid of the thyroid is removed through the lymphatics.

In addition to this thyroïdal tissue the thyroid of some animals contains what is spoken of as parathyroidal tissue, which consists of closely packed columns of small cubical cells without the presence of any alveoli containing colloid. In some animals, as for instance in the

monkey and in man, this parathyroidal tissue is scattered in small masses throughout the substance of the gland ; in others, as the dog, it is accumulated in certain definite masses which are separate and distinguishable from the rest of the thyroid proper and are usually found on the anterior and posterior surfaces of the gland. In other animals, such as rabbits, the parathyroidal tissue, as its name implies, is not situated in the thyroid at all, but forms definite masses in the vicinity of the thyroid. Lastly, most animals possess accessory thyroids, just as accessory spleens and accessory suprarenals are by no means uncommon. In man an accessory thyroid is sometimes found behind the manubrium sterni as well as in other situations, and an enlargement of this body behind the manubrium may give rise to very serious results.

Removal of all thyroidal and parathyroidal tissue in animals and in man is followed inevitably by death, but removal of the thyroid body may or may not cause death ; thus in the dog and in the monkey removal of the thyroid body is almost invariably fatal, but in the rabbit, on the other hand, life is readily maintained after complete removal of the thyroid body. The difference is entirely dependent on the fact that in the case of the dog and monkey the removal of the thyroid gland practically removes the whole of the thyroidal and parathyroidal tissues present in these animals. In the rabbit the removal of the thyroid body does not entail death, inasmuch as the parathyroidal tissue is left behind, but removal of the thyroid and parathyroids in the rabbit is surely followed by death, and removal of the parathyroids alone, leaving the thyroid untouched, is also frequently fatal. Complete removal of the parathyroids in the dog is also followed in a large proportion of cases by death, but not invariably. After partial removal of the thyroid in dogs the survival of the animal is determined by whether one parathyroid be left or not. Experimentally the complete removal of all thyroidal and parathyroidal tissue is followed by the development of a typical series of symptoms, such as tremors, clonic spasms, paralysis, dyspnœa, anæsthesia, apathy, and fall of temperature, and in the case of the carnivora, death results often within a few days, but sometimes life may be prolonged for a fortnight, and in exceptional cases for longer periods. In the monkey similar symptoms are seen, but if the operation be done piecemeal, and if the animal be maintained in a warm atmosphere, life may be prolonged for weeks or months, and, under these circumstances, after the subsidence of the initial severe effects, a further group of symptoms is seen, characterised by loss of hair, emaciation, and some swelling of the subcutaneous tissues, more especially of the face. This latter condition is similar to what is seen in man in the disease known as myxœdema, and resembles still more closely the condition brought about in the human subject by the complete removal of the thyroid, and known as *cachexia strumipriva*. After the removal of the thyroid in dogs, and

at a time when the symptoms produced are at their height, albuminuria, considerable in amount, is also present. Tetany is a symptom frequently seen after complete ablation of the thyroid in man.

After removal of portions of the thyroid experimentally the remaining fragment of thyroid tissue undergoes enlargement, but the hypertrophy is of such a character as to reproduce not the normal structure of the thyroid but the structure of normal parathyroidal tissue. The epithelium lining the alveoli becomes proliferated and papillated, so that the interior of the alveolus is more or less filled with a mass of young actively growing cells, and thus the colloid is encroached upon and soon diminishes and ultimately disappears; there is therefore a great formation of epithelium but no formation of colloid. Removal of the parathyroids alone is followed by hypertrophic changes of a similar kind in the thyroid tissue proper. Recent observations have shown that unilateral removal of the parathyroid and partial thyroidectomies, more especially in dogs, are liable to be followed by exophthalmos and sometimes by enophthalmos. There is a certain amount of evidence to show that the more complete operations are liable to produce enophthalmos, the less complete ones exophthalmos. The structure of the hypertrophied thyroid after partial experimental thyroidectomy is analogous, if not precisely similar, to the structure of the human thyroid in cases of exophthalmic goitre.

The thyroid extract, the active principle of which is in the colloid material, is a body which has a great influence on the metabolic processes of the body, and it is immaterial whether it be administered hypodermically or by the stomach; in both cases the effects are marked. Large doses hypodermically may produce fever, palpitation, dyspnoea, and even delirium, and for this reason it is now usually given by the mouth. Long-continued administration of thyroid extract is said to be followed by evil effects, such as softening and curvature of the long bones, skin eruptions of various kinds, more especially ulceration of the skin of the forehead. Although thyroid extract produces marked physiological and therapeutical effects, it is impossible to maintain indefinitely the life of an animal after thyroidectomy by the administration of thyroid extract; at the most the onset of the symptoms can only be delayed, and notwithstanding the distinct therapeutic effects of this substance in the treatment of myxœdema, it is often of no avail after the removal of the thyroid experimentally. Large doses produce in the monkey exophthalmos, loss of hair, muscular weakness, emaciation, and even death.

Extirpation of one *suprarenal* body is not as a rule followed by death, but some observers have seen a fatal result after such an operation. Usually, however, life is maintained, and the opposite suprarenal undergoes enlargement. Bilateral extirpation of the suprarenals is invariably followed by death, usually within a few days of the opera-

tion. The animal becomes weak, marasmic, drowsy, and the temperature falls, but there are no other marked symptoms. In cases of more prolonged survival after unilateral or bilateral extirpation degenerative changes have been found in the spinal cord, but unquestionably recent observers have not succeeded in confirming the results of earlier operations that removal of the suprarenals was followed by any increase in the pigmentation of the skin. The blood of animals dying after extirpation of these glands is found to possess definite toxic properties. The most important fact, however, with reference to the physiology of the suprarenals is that the medullary portion of the glands contains a substance which has a special stimulating effect on the muscular tissues of the body and more especially on the muscular tissue of the blood-vessels and of the heart. The activity of this substance is such that a quantity estimated at one-millionth the weight of the gland is capable, when injected into the circulation, of producing a marked effect on the blood pressure. This is due to a direct constricting action on the muscular coat of the smaller arteries, and is not only very marked in its amount but it is also very rapid and transitory in its action. It has been suggested that normally the suprarenal elaborates this material and sends it into the circulation through the vein, in that way assisting to maintain the normal tension in the blood-vessels. Notwithstanding that this suprarenal extract produces definite effects when injected into the circulation, its administration by the stomach produces little or no result. Although the function of the suprarenal medulla is thus fairly well understood, physiology is silent as to the action of the cortex.

Very little is known as to the function of the *thymus*, which, however, is a bilateral organ, the two portions being united by connective tissue in the middle line. During embryonic life it is large and active, and it is very probable, as has been suggested by Kölliker and others, that the thymus is the seat of the formation of leucocytes in the embryo and in the fœtus. After birth, however, the thymus dwindles, and in adult life it is often only to be recognised as a mass of fat and fibrous tissue. Experimentally it has been found that extirpation of the gland in animals has been followed by muscular asthenia and œdema; but no structural changes have been noticed in the central or peripheral nervous system. The most interesting fact in the pathology of the thymus is that this gland undergoes hypertrophy in a number of diseases of the blood and of ductless glands, such as exophthalmic goitre, Addison's disease, lymphadenoma, and in some cases of leukæmia.

A portion of the *pituitary body* has a structure analogous to that of the thyroid, and it has been supposed that it is in some way complementary to the thyroid, and that it undergoes enlargement after thyroidectomy. The active principle, however, of pituitary extract has a physiological action somewhat antagonistic to that of the thyroid, and

the only definite fact that we know is that considerable enlargement of the pituitary is associated with the disease acromegaly, and that, further, owing to its position with regard to the optic chiasma, the enlargement of the pituitary is liable to cause bilateral temporal hemianopsia.

Internal secretions of duct glands.—Other glands, such as the liver and the pancreas, as mentioned above, have internal secretions, and in the case of the latter the evidence is peculiarly definite, since ligation of the pancreatic duct produces no ill effects other than those dependent on the absence of the digestive juice in the bowel. Extirpation of three-quarters or seven-eighths of the pancreas, although a very formidable operation, is not followed by death, but removal of the entire pancreas or of the remaining fragment is followed by the development, in the great majority of cases, of a persistent and fatal glycosuria, which, it is asserted, can be checked by the successful grafting of a fragment of the gland. It is supposed that the pancreas elaborates normally a sugar-destroying or glycolytic ferment, which leaves the pancreas through the lymphatics, and by the aid of which the normal metabolism of the sugar of the body is effected; in the absence of the pancreas the sugar that cannot be used accumulates in the blood and is excreted in the urine.

In the case of the kidney, observations of mine have shown that the removal of one entire kidney and half of the other is followed by the excretion of increased amounts of urine and urea, the large quantities of urea being derived from a rapid breaking down of the muscular tissues of the body. It would seem as if the pancreas in some way controls the carbohydrate metabolism, and that the kidney influences the proteid metabolism.

In disease ductless glands having internal secretions may theoretically produce effects, either owing to the cessation of the normal internal secretion, or owing to the normal secretion being produced in abnormal amounts, or possibly owing to the production of an entirely abnormal internal secretion. It is practically certain that cretinism and myxœdema are dependent upon the cessation of the normal thyroidal secretion. There is an accumulating mass of evidence that Graves' disease may be dependent upon an excessive activity of the thyroid, but there are difficulties in the way of complete acceptance of this view. Some forms of diabetes may be dependent upon an excessive activity of the glycogenic function of the liver, and this is essentially an internal secretion. Other forms of diabetes are doubtless associated with pancreatic disease. In the case of the suprarenal it is impossible at present to account for all the phenomena of Addison's disease on the hypothesis of a mere arrest in the formation of the tonus-producing substance elaborated by the medulla of this gland. The great and peculiar cardiac and circulatory weakness of this disease may, however, be dependent on the internal secretion of this gland being arrested.

JOHN ROSE BRADFORD.

CRETINISM—MYXŒDEMA

Cretinism and myxœdema are diseases which, although occurring at different periods of life, are yet closely allied. Cretinism is a chronic disorder chiefly of females, occurring both endemically and sporadically, characterised by arrest of growth with a varying degree of mental impairment and associated with absence or lesions of the thyroid body.

Cretinism occurs in all parts of the world, but it is more especially prevalent and endemic in certain mountainous districts, as in Switzerland. *Endemic cretinism* is almost unknown in England, but it is said to occur in some parts of Scotland. It is especially found in places where goitre is common, but the latter may be prevalent without cretinism, and this is the case in many parts of England, amongst others on the Sussex downs. Both goitre and cretinism have been connected by many authorities with peculiarities of the soil, as for instance limestone rocks. Endemic cretinism is often associated not only with the presence of goitre in the cretin, but with the prevalence of goitre unaccompanied with cretinism in other members of the family. It is probable that the prevalence of endemic cretinism in certain localities is not entirely dependent on the formation of the soil or on the climate, but is partly kept up by heredity, inter-marriage being common in some remote districts where the disease exists.

Sporadic cretinism is essentially similar in its characters to endemic cretinism, except in so far that it has no relation to locality, and cases are not uncommon in England.

The **characteristic features** of cretinism are sometimes present at birth, and cases of foetal cretinism have been described, but it is rare for the malady to be recognised before from the sixth to the tenth month; and it is unusual for the condition to develop after the seventh year. The child is weak, the abdomen large and pendulous, the limbs are small, the extremities large, especially the hands, which are frequently broad and flattened, such as are seen in myxœdema. The child often has a peculiar hollow cry, the teeth are cut late, decay prematurely and fall out. The power of walking is developed very late, frequently not until six or seven years of age, and articulate speech may be absent until then. One of the most characteristic features of the disease is the arrest of

growth, so that even an adult cretin of four or five and twenty years of age may have the stature of a child of three or four years. Puberty is late in its appearance and the genital organs are very feebly developed. The head is large, often brachycephalic, the hair of the scalp is scanty, dry, coarse and bristly, and on the pubes and the rest of the body is often absent. The face resembles the Mongolian type, it is square and large with thick lips and flattened nose; the eyelashes are scanty, the skin yellowish-brown, dry, coarse and rough. The tongue is large, sometimes protruding, and saliva frequently dribbles from the mouth. The neck is short and thick, and in the supraclavicular fossæ there are often large masses of fat forming prominent swellings. The thyroid gland is often absent in cases of sporadic cretinism, and in the endemic form the great majority of cretins are goitrous. The goitre is frequently fibrocystic, and hence, in spite of the enlargement, there is probably but little normal thyroid substance present. The degree of mental impairment varies greatly. In some there is complete absence of the power of speech and of all intellectual faculties; in others there is some power of articulation, and they have sufficient intelligence to attend to the bodily wants. In still slighter cases the patients have sufficient intelligence to do light work. Many cretins, however, are dirty in their habits, and there may be complete absence of all sexual instinct. Cretins not uncommonly suffer from epileptiform seizures, and hernia is said to be common; the body temperature is subnormal and the circulation feeble, the extremities being cold.

The most remarkable feature about the skull is the fact that there is arrested growth and premature ossification of the bones that develop in cartilage, hence the basi-sphenoid and the basi-occipital, which should not unite until from the fifteenth to the twentieth year, may be united at birth. The portions of the skull, however, formed in membrane are well developed. Owing to the premature ossification of the basi-sphenoid and the basi-occipital, the relations of the medulla and the cerebellum to the brain become altered, so that the crura, pons, and medulla are placed much more vertically than normal.

The spine is frequently curved, so that the cervical and upper dorsal regions are convex backwards and the lumbar region presents a deep concavity. The clavicle (a membrane bone) is well developed, but all the long bones are shortened and the epiphyses are much enlarged in relation to the shaft, and may in extreme cases of foetal cretinism constitute as much as three-quarters of the entire

length of the bone. The bones are well ossified and present curvatures which are exaggerations of the normal ones. The most characteristic feature of the long bones on section is that fibrous tissue grows in from the periosteum between the epiphyses and the shaft, and it is perhaps in part owing to these ingrowths from the periosteum that the arrest in the growth of the bones occurs. The defect is mainly due to the fact that the process of ossification in the cartilage does not take place in a normal fashion but in a manner similar to rickets. The cartilage cells in the ossifying line do not become arranged in the normal regular rows parallel to the length of the bone, but are scattered irregularly, and thus the bone does not grow in length, but a large massive epiphysis is formed instead. The ribs, where they join the costal cartilages, are deeply cupped, so that the cartilages are enveloped by bone.

In cretinism the incidence of the morbid process is mainly on the connective tissues of the body, and this is especially seen in the ingrowth of the periosteum in the long bones described above.

Treatment.—Cases of goitre, and children born in the locality should be removed from districts where cretinism is endemic. Until recently cretinism was considered incurable, and it probably is so still in advanced cases. In slight cases and in those seen early, great benefit may be derived from the administration of thyroid extract.

MYXŒDEMA

Myxœdema, when first recognised in 1875 by Sir William Gull, was described by him as “a cretinoid state supervening in adult life in women.” It is a malady closely related to cretinism, occurring in adults from thirty-five to fifty years of age, more usually in females and in those who have borne families; only about 10 per cent of all cases being met with in men.

The condition has been seen as late as seventy years of age, but is very infrequent in youth and early adult life. An hereditary predisposition is doubtful.

Symptoms.—The onset of the disease is gradual, though its first recognition by the patient may be after some acute illness. The earlier symptoms are extreme debility and great disinclination to exertion, headache and marked susceptibility to cold. An acute onset with shivering has been recorded. In an advanced case the body is swollen, but does not pit on pressure, the spurious appearance of œdema being dependent, as in cretinism, on a thickening of the skin and subcutaneous tissue, and partly on the

presence of superabundant fat. Soft fatty swellings are especially marked above the clavicles and are similar to those seen in cretins. The skin is very dry and harsh. The hands and feet are large, and very broad; the bones, however, are not enlarged, the increase in size being dependent on the swelling of the subcutaneous and fibrous tissues. The skin of the face is usually puffy and slightly yellowish, with the exception of the malar area, where there is often very considerable and persistent flushing, so that the combination of the swollen expressionless features with the malar flush and the surrounding yellowish skin is very characteristic. The eyelids are often extremely puffy and translucent, and the eyebrows raised. The lips are swollen and purplish, the nose broad and ears large. The swelling is not limited to the skin and subcutaneous tissue, but is also to be detected in the mucous membrane of the mouth, so that the soft palate is often swollen and the tongue large. The hair becomes very dry and sparse, baldness being not uncommon. The loss of hair is not confined to the scalp, but affects all those portions of the body where hair is normally present. Brownish crusts are seen on the scalp and back of the neck. The circulation is generally depressed, the pulse slow and soft, the heart's action feeble with liability to syncope and palpitation. The appetite is poor, and constipation or diarrhoea is frequent. Some degree of anæmia is usually present. The temperature is subnormal and may be as low as 96° F., and the extremities are frequently cold. The urine is said to be often diminished in quantity, and although it usually contains no albumen or sugar yet traces of the former are not uncommon, and glycosuria has been found to coexist with myxœdema. Severe hæmorrhage from the nose or uterus, or even from the extraction of a tooth, sometimes occurs. Menstruation is usually regular and may be excessive, especially in the early stages of the malady; but when the disease is fully established the catamenia may cease and sterility is usual, though under the influence of thyroid treatment the former may reappear and pregnancy is possible. It is stated that when pregnancy occurs under these circumstances the general swelling of the body may undergo diminution, but apart from this condition fluctuations in the degree of subcutaneous swelling are not uncommon.

The movements of the body are slow, the speech is extraordinarily slow, deliberate, and monotonous, so that often the disease can be diagnosed from the voice. The movements of the hands are also especially slow and awkward. Mentally the patients fail in their memory, are apathetic but frequently irritable and

suspicious, and occasionally are possessed of delusions or become definitely insane. In some cases there is a risk of suicide.

Morbid anatomy.—The thyroid gland is small, atrophied and fibroid. In advanced cases the gland consists mainly of fibrous tissue, the remains of the vesicles being represented by scattered cells. In less advanced cases the epithelium lining the vesicles undergoes proliferation but the colloid disappears. It is not unusual to find the kidneys granular, together with considerable cardiac hypertrophy and arterial degeneration, the vessels being thickened, and this no doubt is partly responsible for the view at one time held that cases of myxœdema were only anomalous cases of Bright's disease. The thymus and pituitary glands have both been found enlarged. The swollen condition of the body is dependent on an excessive amount of subcutaneous connective or adipose tissue, and is somewhat similar to the condition brought about experimentally by removal of the thyroid. In so-called experimental myxœdema the swelling is not so generalised as that seen in the natural disease, being usually limited to the face and parotid regions. It is not due to a mere excess of mucin, but rather to the formation of young fibrous tissue in excessive amount, and hence to a certain extent the name myxœdema is a misnomer. Changes of a degenerative character, vacuolation, slight fibrosis, minute hæmorrhages, etc., have been described in the cerebral cortex and in the spinal cord, but more extended observations are required. That the nerve centres are altered is probable, having regard to the mental and other nervous symptoms.

In a few cases myxœdema has been known to follow exophthalmic goitre, and it is not uncommon for the myxœdematous swelling and other symptoms to develop at a time when the thyroid body is still enlarged and before some or all of the symptoms of exophthalmic goitre have passed away. Even in these cases, however, when the myxœdematous condition is fully established the thyroid body is atrophied. Graves' disease and myxœdema have been met with in different members of the same family. Several cases are on record where, in addition to the general symptoms of myxœdema, those of acromegaly were superadded with changes in the pituitary body.

Myxœdema is not only allied to cretinism but also to *cachexia strumipriva*, a condition described by Kocher as produced by complete removal of the thyroid in the human subject. Such patients soon become dull, apathetic, slow, and the characteristic swelling of the body seen in cretinism and myxœdema is developed. The

only prominent difference perhaps is the fact that whereas tetany is not uncommon as a result of the removal of the thyroid in the human subject, it is seldom observed in myxœdema.

The duration of the disease is to be measured by years, and death usually results from some intercurrent pulmonary affection, such as bronchitis or pneumonia.

The evidence that myxœdema is dependent on loss of function of the thyroid does not rest simply on the facts of the morbid anatomy of the disease, inasmuch as the treatment of cases of myxœdema with thyroid extract is followed by the subsidence of all the characteristic features of the disease and by restoration to good health. Under the influence of thyroid extract the swelling disappears, the hair begins to grow, and even in cases of myxœdema where complete baldness was present, abundant hair may subsequently develop. The mental faculties recover their vigour, and the same applies to the bodily functions. A marked loss of weight accompanies this treatment. At first the thyroid extract was administered hypodermically, but it was subsequently found that the same beneficial results were obtained when it was given by the stomach. At the present time the treatment of myxœdema by thyroid extract is so satisfactory that little other treatment is required except to avoid exposure to cold. The dry thyroid powder of the pharmacopœia should be given in doses of from five to ten grains daily. Large doses of thyroid extract produce pyrexia, tachycardia, palpitation, and sometimes delirium or even tetany, more especially when administered hypodermically, so that it is well to give the substance at first in small doses and by the stomach. Glycosuria has also been observed as a result of excessive doses of thyroid extract, and it is said that the long-continued administration of this substance may lead to softening and curvature of the long bones. The patient, however, must continue the administration of the thyroid extract in diminished doses, as the cessation of its administration will be followed by the return of the symptoms. Myxœdematous patients should be carefully protected from the cold, and frequent warm bathing should be enjoined. The action of the skin may also be promoted by the administration of pilocarpin.

JOHN ROSE BRADFORD.

EXOPHTHALMIC GOITRE

SYN. GRAVES' DISEASE; BASEDOW'S DISEASE

The malady known by these names is characterised by enlargement of the thyroid body, protrusion of the eyeballs, extreme nervousness, palpitation, and tremor. In addition to these the more constant phenomena, gastro-intestinal disturbance, mental derangement and disturbances of nutrition, such as emaciation and pigmentation of the skin, are not uncommon.

The disease, like myxœdema, is most frequent in women, and more especially between puberty and forty years of age; it may, however, occur later, and sometimes in children as young as three years old, and it is very rare in men. In a hundred cases observed by Dr. Hector Mackenzie there were only five males.

The **etiology** is obscure. It is known to be more prevalent in some districts than in others; it may affect more than one member of the same family, and it has frequently been traced to mental anxiety, over-work or shock, and it has been asserted that it may follow fright; it also occasionally occurs during convalescence from acute diseases. It is sometimes associated with nervous disorders, more especially epilepsy, insanity, and hysteria, and it is not uncommon to see exophthalmic goitre develop in the epileptic. Pregnancy is held by many to have a causal relation with this disease. Some observers, however, consider that its symptoms, like myxœdema, undergo improvement during pregnancy.

Symptoms.—Sometimes, though not often, the enlargement of the thyroid is the first symptom noted, in other cases extreme nervousness and tremor are the earliest manifestations of the disease. In the majority palpitation and cardiac distress are the symptoms for which advice is sought; in a few the patient comes under observation on account of undue prominence of one or both eyes. Great differences are exhibited in the degree to which these several symptoms are developed in different cases.

The *enlargement of the thyroid* varies much in amount; it is usually considerable, and although involving the whole of the gland, the right side is perhaps generally somewhat larger than the left. The enlargement of the thyroid may be so great as to cause respiratory distress, but this, when it is present, usually arises from

another cause. The enlargement is soft, or hard knotty and irregular; there may be visible pulsation of the organ, and on palpation a thrill can be felt either over the whole thyroid or more especially at the upper and lower borders, where the superior and inferior thyroid arteries enter the gland. A loud systolic bruit is usually to be heard. The enlargement of the gland varies in amount from time to time, both as a result of treatment and spontaneously; in some cases, where the other symptoms of the disease are well marked, the thyroid enlargement is inconspicuous or even completely absent. The enlargement is not always confined to the thyroid body proper, but may involve in addition the accessory thyroids, and in this way may produce extremely dangerous results, as for instance when an accessory thyroid situated behind the manubrium undergoes enlargement and causes very severe dyspnoea by pressure on the trachea.

Exophthalmos.—Undue prominence of the eyes is a characteristic feature of Graves' disease. It varies in degree, and the protrusion may be so great that the cornea undergoes ulceration from the want of protection of the eyelids. The exophthalmos is usually present in both eyes, but frequently to a different extent, and it has been thought that the prominence is more marked on the side on which the thyroid enlargement is the greater. Occasionally cases are seen of unilateral exophthalmos. The prominence of the eyes is partly apparent and dependent on widening of the palpebral fissure and retraction of the upper eyelid. The retraction of the upper lid and consequent appearance of a ring of the sclerotic around the cornea (Stellwag's sign) is probably dependent on spasm of the levator palpebræ; and the over-action of the muscle of Müller and of the involuntary muscular tissue in the eyelids which are under the control of the sympathetic cause the widening of the palpebral fissure, which is similar to that seen experimentally on excitation of the cervical sympathetic. The prominence of the eyes is not entirely due to this, for in addition there is a true exophthalmos; this may be brought about in part by weakness of the external ocular muscles leading to proptosis, and partly perhaps as a result of vasomotor changes. The exophthalmos is certainly not due to any mere excess of fat in the orbital fossa. It is present, although in greatly diminished amount, after death. In addition to the above, in Graves' disease there is a want of co-ordination between the action of the upper eyelid and the recti muscles, so that on looking down the eyelid and the eyeball do not move together, but

the eyelid lags behind the eyeball ; this is known as Von Graefe's sign, and is probably not simply dependent on spasm of the levator palpebræ. This sign may be well marked when the exophthalmos is slight in amount, and it is of considerable diagnostic importance. The degree of exophthalmos varies from time to time ; it may be present to a high degree with comparatively slight enlargement of the thyroid body.

The pupil in this malady is usually unaffected. In some cases the weakness of the external ocular muscles is considerable, and diplopia from this cause is not uncommon. In some cases complete external ophthalmoplegia may be present.

Optic neuritis and optic atrophy are sometimes seen in cases of exophthalmic goitre, and rarely complete amaurosis may be met with.

Patients frequently complain of flushing of the surface and sweating, and to this circumstance is ascribed the diminished electrical resistance that the body has been found to offer.

Circulatory symptoms.—Palpitation is a cardinal feature of this disease. The pulse is usually over 100, even during complete rest, and the pulse rate may reach 160 or more. The slightest exertion or excitement will cause extreme palpitation and tachycardia. Exceptions to this statement must be admitted to occur ; for undoubted cases of the disease are seen without increase in pulse-rate, and this may be said to be the rule in children. The heart's action is usually regular and the pulse presents no characteristic qualities. Forcible pulsation of the vessels of the neck is a prominent feature of the disease. The heart shows signs of slight enlargement, the apex being displaced to a moderate extent downwards and outwards, and the impulse is somewhat heaving in character. On auscultation a blowing systolic murmur is frequently heard both at the base and the apex. Occasionally definite valvular disease co-exists, but more usually the murmur is dependent on anæmia or on dilatation consequent on hypertrophy.

Epistaxis and hæmorrhages from the mucous membranes are not infrequent early symptoms.

Tremor.—Tremor of the limbs is a marked feature of most cases of Graves' disease and is remarkable as a rule for its fine character ; it is present to a slight extent during rest, and greatly exaggerated on exertion. It resembles senile tremor and that of alcoholism. Severe cramps are complained of, and weakness of the extremities dependent on peripheral neuritis may occur.

Extreme nervousness is a marked characteristic of the disease and may be the earliest symptom.

In all severe cases *emaciation*, *anæmia*, *muscular debility*, and slight *pyrexia* are present, and the emaciation is sometimes extreme in amount, resembling that seen in *anorexia nervosa* and in malignant disease. Delirium is not uncommon, and occasionally actual mania is seen, upon which death usually follows.

One of the most remarkable symptoms of the disease is *dyspnœa*. This is usually paroxysmal and is accompanied by an exacerbation in the severity of the palpitation. It very closely resembles that seen experimentally after removal of the thyroid, and that occasionally seen in the human subject after operations on the thyroid in Graves' disease or even in other goitres. The respirations are hurried to forty or fifty a minute, both the inspiration and the expiration being deepened. The breathing closely resembles the hissing respiration seen in some forms of uræmia, and also the attacks of dyspnœa seen in leukæmia. Death may occur during the paroxysm of dyspnœa. The cause of this dyspnœa is obscure; it certainly does not depend only on the pressure of the tumour on the trachea, as it may occur and cause death when the thyroid enlargement is slight. It is possible that it may be due to pressure on the nerves of the larynx, but it is more probable that it is of toxic origin and due to the disturbance in the metabolic activity of the gland; or to the action of the thyroid internal secretion on the respiratory centres in the bulb. It is remarkable that the same dyspnœa should be seen not only after the removal of either a portion or of the entire gland, but also when the gland is enlarged as in Graves' disease.

Vomiting is occasionally present and is, on the whole, a severe and dangerous symptom. Death has occurred from vomiting in cases of Graves' disease; and this where, although the tremor and the nervousness were present to a high degree, yet the exophthalmos and the enlargement of the thyroid were very slight in amount. *Diarrhœa* is also occasionally marked.

Pigmentation of the skin is not uncommon, and the skin of the abdomen may be as deeply pigmented in this malady as in some cases of Addison's disease. It is also similar to that seen occasionally in diabetes, cirrhosis of the liver, and tuberculous peritonitis. Patches of leucoderma are also not uncommon. Scleroderma has also been seen associated with Graves' disease. The hair of these patients is usually dry and scanty.

The *urine* may contain a trace of albumen. The *catamenia* are generally irregular; both amenorrhœa and menorrhagia are frequent.

Prognosis.—Graves' disease is frequently fatal ; death usually results from asthenia, the patient being worn out by the palpitation, the excitement and nervousness. Sometimes acute mania develops and death rapidly ensues. The same may result from the dyspnoea or from uncontrollable vomiting. It is not rare for death to occur with great suddenness in cases which do not give rise to much anxiety, and it is important to bear in mind that this may happen even in cases where the exophthalmos and thyroid enlargement are both slight in amount. The disease not uncommonly undergoes arrest. More frequently probably it undergoes amelioration or even cure, but in such cases relapses from time to time occur. The most interesting sequel of Graves' disease is myxœdema, and many cases have now been recorded where myxœdema has supervened in later life in instances where exophthalmic goitre was present at a former period. Diabetes mellitus has been known to follow on this affection. According to Dr. Mackenzie the mortality of the disease is about 25 per cent in well-marked cases.

Morbid anatomy.—The body is generally greatly emaciated ; the thyroid is considerably enlarged ; the thymus is found persistent and often much larger than usual ; the heart is moderately hypertrophied, and frequently the mesenteric glands and the spleen are swollen. In the thyroid there is no striking evidence of any great or exceptional increase in the size of the blood-vessels ; they are probably only enlarged to a degree equivalent to the enlargement of the gland itself.

Microscopically the thyroid shows great increase in the number of the cells lining the alveoli ; they are proliferated and thrown into folds ; the epithelium has become columnar and the alveoli are often filled with masses of cells. There is no appreciable increase in the colloid substance and the important point is that the hypertrophied thyroid of Graves' disease reproduces the structure of the normal parathyroidal tissue rather than that of the normal thyroid. Further, the changes the gland undergoes in this malady are essentially similar to those produced experimentally by removal of a portion of the thyroid. After partial thyroidectomy the remaining thyroidal tissue undergoes hypertrophy, but it does not reproduce exactly normal thyroidal tissue but parathyroidal tissue similar to that seen in exophthalmic goitre.

The persistence and enlargement of the thymus in Graves' disease is similar to that seen in Addison's disease, lymphadenoma, and in some cases of leukæmia. Microscopically the enlarged thymus reveals the structure of the normal thymus. The spleen

and lymphatic glands are sometimes increased in size. Some observers have described hypertrophy of the sympathetic ganglia and also minute hæmorrhages in the central nervous system.

Pathology.—No satisfactory explanation of Graves' disease has yet been propounded. In some ways the symptoms resemble those produced by an excessive dose of thyroid extract; in this way palpitation and exophthalmos can both be produced, and hence a tempting hypothesis is that, owing to the hypertrophy of the thyroid, the economy receives an undue amount of thyroid secretion; in other words, that the disease is a toxæmia dependent on the excessive production of the active principle of the thyroid body. But the symptoms do not vary in their severity with the degree of enlargement of the thyroid; in many cases where the exophthalmos and cardio-vascular phenomena are most marked, enlargement of the gland is quite moderate in amount. Further, simple parenchymatous goitres of large size are often seen with a microscopic structure closely similar, if not identical with, that found in Graves' disease, and yet the patient presents none of the symptoms of this malady. Some observers have thought that inasmuch as the thyroid in Graves' disease has a similar structure to that seen in the hypertrophied thyroid produced experimentally after thyroidectomy, that the enlargement is not primary but secondary, and dependent on an increased demand by the body for the active principle of the thyroid. The fact that Graves' disease is sometimes followed by myxœdema, and that in myxœdema the thyroid is atrophied, is an argument that has been used in favour of the disease being dependent on the hypertrophy of this gland. Since the disease frequently occurs in patients with a neurotic diathesis, or where other members of the family have suffered from disease of the nervous system, and also as patients with Graves' disease sometimes develop as complications diseases of the nervous system, such as ophthalmoplegia and progressive muscular atrophy, it has been thought that the malady is primarily one of the nervous system, but there is no sound experimental evidence that lesions of the nervous system—cerebrospinal or sympathetic—can produce anything analogous to exophthalmic goitre.

Diagnosis.—Diagnosis of the disease in typical cases is easy; it is only where some of the cardinal symptoms are absent that difficulties are experienced. The nervousness and trembling, the palpitation and tachycardia and the ocular signs, are most reliable in the absence of exophthalmos and goitre. Difficulties occasionally arise from the presence in cases of simple goitre of such compli-

cations as pericarditis or endocarditis, when the significance of the tachycardia may be misinterpreted.

Treatment.—The general hygiene of the patient requires most careful attention. Absolute rest and freedom from all excitement are essential in severe cases ; but gentle exercise, stopping short of the slightest fatigue, is often beneficial when the malady is less advanced. Change of air, such as a sea voyage, or residence at a moderate altitude may be tried.

The diet should be confined to easily digested food ; alcohol should be avoided, and tea and coffee allowed in very small quantities.

Galvanism and faradism have been strongly recommended, with the view of modifying the action of the sympathetic nerves, one pole being applied to the back of the neck and the other over the course of the nerve, or over the thyroid, eyes, or heart.

Applications of cold to the gland or precordia by means of ice or Leiter's tubes have been employed with benefit.

Among drugs, sedatives such as opium or the bromides are of but little use. Digitalis is very uncertain ; some cases distinctly improve with it, but unless it do good at once it should not be continued. Belladonna is the drug that has been credited as the most successful remedial agent. Doses of 10 minims or more of the tincture are given, but care must be taken that the toxic effects of this drug are not produced, as sometimes the delirium due to belladonna has been ascribed to the disease itself. Some authorities speak highly of the results of systematic purging with phosphate of soda ; personally I have not seen much benefit from its use. Tonics, such as iron and arsenic, are very necessary, and citrate of potash in an effervescing form often allays the vomiting.

Thyroid and thymus extracts appear to be valueless.

Venesection has been recommended for the relief of the dyspnœa.

Owing to the frequency with which the disease tends to improve, it is not easy to estimate the benefit from treatment. Iodine and the iodides are said to intensify or even induce the symptoms.

Of late years operative interference has been recommended in severe cases, such as division of the isthmus or removal of a portion of the goitre, or ligature of the thyroid arteries. It must be remembered, however, that the former operations may be followed within a few hours by violent dyspnœa, palpitation, and rapid death. Nevertheless where the disease is present in a severe form

and in selected cases operative interference may be justifiably recommended, and many cases of improvement, with complete subsidence of all symptoms, have been described after partial thyroidectomy. Division or resection of the cervical sympathetic has also been recommended, and marked benefit from this treatment has been recorded; but it is a procedure that is not unattended with considerable risk.

JOHN ROSE BRADFORD.

ADDISON'S DISEASE

This disease, first described by Dr. Addison in 1855, is an affection of the suprarenals, characterised by excessive weakness, debility, wasting, gastro-intestinal disturbance, and pigmentation of the skin and mucous membranes.

The disease more especially affects males, usually in adult life and about the age of thirty: it is very rare in old age; a few cases in infants and children have been described. Although more common in men, it is not very unusual in women.

The malady has been known to follow injuries of the abdomen and of the back; and it is possible that in some cases the disease arises as a remote sequel to the effects of hæmorrhage into the suprarenal during birth, as this condition has been found in the suprarenals of still-born children. Severe mental strain has been recognised as an antecedent.

Morbid anatomy.—Although the characteristic symptoms of Addison's disease are found associated with several lesions of the suprarenals, yet the malady is far more commonly connected with tuberculous disease of these glands, which may occur with caries of the spine in the lumbar region. *Tuberculosis* of the suprarenal is, however, not synonymous with Addison's disease, as tuberculous deposits are frequently found in these glands associated with the presence of tuberculosis elsewhere, without the presence of any symptoms of Addison's disease. The tuberculous deposits, which may be limited to the suprarenals, never occur in the miliary form. Besides tuberculous caseation, *fibrosis* of the gland and simple *atrophy*, so extreme that it may be difficult for the gland to be

recognised post-mortem, are not uncommon lesions of these organs in Addison's disease. Occasionally *malignant disease* of the suprarenals is found associated with the symptoms of Addison's disease. Exceptionally in this malady the glands themselves are found to be healthy, but are embedded in a mass of inflammatory tissue or of malignant disease involving all the surrounding structures, and especially the sympathetic nerves and ganglia.

The caseation and fibro-caseous deposit met with in this disease begin in the medulla. The caseous matter may break down as a result of softening, or, on the other hand, it may become cretaceous. The suprarenal bodies may be considerably enlarged and nodular, and there may be a considerable amount of chronic inflammation in the surrounding structures, leading to matting together of the glands and the surrounding sympathetic ganglia and nerves. The lesion is usually bilateral, but occasionally unilateral. Tubercle bacilli have been found in the caseous mass. It is important to bear in mind that when the suprarenals are found apparently healthy in the midst of a mass of malignant growth that the circulation through the gland is probably very greatly interfered with, and that under these circumstances effects very similar to those produced by the destruction of the gland itself may be produced.

Besides the lesions of the suprarenals, the thymus is often found persistent, and the abdominal and mesenteric glands and the lymphatic structures in the intestine enlarged. The spleen may be enlarged. No definite and uniform changes have been found in the sympathetic ganglia, and no constant changes in the central nervous system. Pigmentation of the serous membranes has been occasionally seen; and the intestinal mucosa may be the seat of an extensive pigmentary deposit. Tuberculous lesions may be found in other parts, as in the lungs or in the vertebræ, but cases are not uncommon where the tubercle is confined to the suprarenal bodies.

Symptoms.—The disease is very insidious in its onset, and as a rule this cannot be accurately dated, the patient simply suffering from increasing weakness and extreme lassitude without any obvious cause. The general health, in fact, becomes less good, the patient feels apathetic, and the appetite is much diminished. Soon a progressive wasting is noticed, and the patient becomes distinctly asthenic. The asthenia increases until the end, although the course of the malady is not uniformly downwards; occasionally remissions and exacerbations in the gravity of the symptoms are observed. Early in the disease the patient may suffer from pain in

the epigastrium of varying degrees of severity. Nausea and vomiting soon become marked, and they may be present in cases where the patient does not complain of pain. Diarrhœa also is a not uncommon symptom. One of the most characteristic phenomena is a circulatory weakness, so that the slightest exertion is liable to cause syncope, and the patient has an extremely soft, compressible pulse, which, when the disease is fully established, may be even imperceptible at the wrist, and the exertion of sitting up in bed may lead to fatal syncope. It is interesting to observe that the weakness which is a cardinal feature of the disease is therefore not limited to the voluntary muscles, but affects also the heart muscle and perhaps the muscular coats of the arteries. The weakness of the circulation is shown not only by the tendency to syncope, but also by the presence of palpitation, vertigo, headache, and frequent yawning. The body temperature is usually subnormal.

The most remarkable and striking symptom of Addison's disease and the one by which the malady is usually recognised is the pigmentation. This is of such a character as to cause a patient of the whiter races to approximate in colour to one of the darker races of mankind. The pigmentation may vary from a faint brownish discoloration to quite a dark hue; it is fairly uniform in its distribution; the pigmented area fades off gradually and not suddenly into the surrounding normally coloured skin. The pigmentation is more marked on exposed surfaces of the body, such as the skin of the face, neck, and hands, than on covered parts; it also tends to be more apparent where the skin is thin, as for instance the front of the thighs. It is more noticeable where pigment is present normally, as in the areolæ, the axillæ, and around the umbilicus, and it is apt to be developed where pressure is exerted, as, for instance, below or above the knees, where the patient ties garters, and along the spine; scars are not liable to become pigmented. The pigment is not limited to the skin but is present in the mucous membranes, more especially the inside of the lips, cheeks, and on the tongue, and it is said that the mucous membrane covering the labia and vagina is sometimes pigmented. It is not uncommon for areas of darker pigment to be developed in the midst of the more uniform brown mottling characteristic of the disease. The pigment is situated in the Malpighian layer of the skin, just as it is in the darker races of mankind. The observation of the characteristic pigmentation is frequently the means by which the disease, until then obscure, is recognised. It is possible that some cases of disease of the supra-

renals, with the symptoms of Addison's disease, but without pigmentation, are occasionally seen.

Anæmia is not a marked feature of the disease, and, according to Osler, the diminution of blood corpuscles never exceeds 50 per cent. The sclerotics remain pearly white, and in that way present a marked contrast to the pigmented skin of the face.

The urine is usually of the normal colour, but occasionally urobilin and hæmatoporphyrin are present in abnormal amounts, and melanin has been described in exceptional instances.

The malady, which is always fatal, is said to last from one to three years, the average duration being eighteen months. Cases, however, are occasionally seen of longer extent, whilst others may run an acute course of only a few weeks. Death usually results from asthenia, sometimes from syncope. Delirium and convulsions may also occur as terminal phenomena.

Pathology.—Two views have been held with regard to the nature of Addison's disease. According to the one the malady is dependent on the simple destruction of the suprarenal bodies; according to the other it is dependent rather on secondary changes in the abdominal sympathetic system, produced perhaps by the suprarenal disease. The main difficulty in the acceptance of the first view lies in the fact that cases have occurred in which the suprarenals have been destroyed by malignant disease, or even by tuberculous disease, without the symptoms of Addison's disease supervening. Many of these cases, however, may be explained on the hypothesis that the course of the disease was rapid and did not allow sufficient time for the symptoms of Addison's disease to become developed; and the possibility of supernumerary adrenals must not be forgotten. Another difficulty that presents itself is that cases of Addison's disease have been recorded where the suprarenals, although surrounded by growth, have yet seemed healthy; it is possible, however, that in these cases the function of the glands, more especially the circulation through them, was very seriously interfered with, and that in this way, although the glands were present, they were not functional. The nervous theory was put forward to explain these facts, and also because the abdominal sympathetic was frequently involved either in dense fibrous tissue or in malignant growths. The nervous theory, however, is untenable in the light of recent knowledge of the physiology of the suprarenals, and also from the numerous cases in which the abdominal ganglia have been found normal in cases of Addison's disease. The malady is unquestionably due to the cessation of the

function of the suprarenals, but whether it is a toxæmia dependent on the retention in the economy of toxic bodies that should be destroyed by the activity of the suprarenals, or, on the other hand, whether it is due to an enfeeblement of the body generally on account of the loss of the internal secretion elaborated by the suprarenals, is not as yet thoroughly established. Dr. Mote has suggested that these organs are concerned in the excretion of the toxic products of the metabolism of the central nervous system, *e.g.* neurine. These glands in Addison's disease have not been found to contain an active extract, but, on the other hand, the administration of the suprarenal extract in cases of Addison's disease has not been followed by the marked beneficial effects that are known to follow the administration of thyroid extract in myxœdema. In some respects the symptoms of Addison's disease, especially the weakness, are similar to the effects seen experimentally after removal of the suprarenals.

The **diagnosis** of Addison's disease is usually difficult, especially in the early stages, before the pigmentation is marked, and it can only be diagnosed by the exclusion of a great number of other diseases, such as gastritis, malignant disease, etc. Pigmentation is the most noticeable sign, but there are many diseases in which pigmentation, somewhat similar to that seen in Addison's disease, is found. Persons of uncleanly habits who have led a life of exposure are liable to a brown discoloration of the skin dependent on phthiriasis. This, however, is most marked, not on the exposed, but on the covered portions of the body. Arsenical pigmentation has been mistaken for the disease. Leucoderma and melanoderma produce a superficial resemblance to the pigmentation of Addison's disease, but here the separation between the pigmented and the non-pigmented portions of the skin is always abrupt, whilst in Addison's disease the pigmented area fades away into the non-pigmented. In pregnancy or malarial cachexia there may be considerable pigmentation. Cases of tuberculosis, and more especially of tuberculous peritonitis, are often associated with considerable brown pigmentation of the abdomen and face. In rare cases of hepatic cirrhosis pigmentation is seen, and there is a particular variety of diabetes associated with hypertrophic cirrhosis, the "*diabète bronzé*" of the French, in which pigmentation, especially of the abdomen, is a conspicuous symptom. Pigmentation may, however, be found in the diabetic with or without hypertrophic cirrhosis of the liver. In exophthalmic goitre pigmentation, somewhat similar to that of Addison's disease, is

sometimes observed. To this bronzing of the integuments the term "hæmochromatosis" has been applied (see p. 189).

The extreme and progressive weakness, the vomiting and the exceeding softness of the pulse, are the other most important diagnostic symptoms.

Treatment.—This is entirely palliative. In severe cases absolute rest in bed is necessary, more especially to avoid syncope, and in all cases great care should be taken to prevent any sudden movement in bed. Strong purgatives must not be given. Simple nutritious diet is very necessary. Bismuth and opium may be used to relieve the vomiting and diarrhœa, and tonics, such as strychnia, arsenic, and iron are most useful. Suprarenal extract may be given by the stomach, but its administration has not been followed by any strikingly beneficial results—perhaps for the want of a reliable preparation of the medullary part of the gland—although a few cases have been described where the symptoms were temporarily alleviated, and there is some evidence to show that suprarenal extract, unlike thyroid extract, is not so efficient when administered by the stomach as when it is injected subcutaneously.

JOHN ROSE BRADFORD.

OBESITY

The over-development of adipose tissue throughout the body cannot be said to constitute disease until the due performance of the bodily functions is thereby interfered with, and to this degree of fatness the term obesity is applied. Localised fatty overgrowths such as are frequently seen above the clavicles and in the axillæ in cases of sporadic cretinism and in myxœdema; or the symmetrical lipomata occasionally met with about the back of the neck, particularly in alcoholic men, are not included within the scope of the term, although these by their position may give rise to inconvenience. Rather is it a form of general malnutrition characterised by an enormous formation of fat in the situations where this tissue is normally found, both subcutaneously and within the cavities of the trunk. In certain regions, however, such as the buttocks, the throat, the neck and chin, or over the abdomen, the fat may be preponderantly developed, even beyond that of the general surface.

Adipose tissue is first recognisable in the embryo at about the middle of the fourth month of foetal life, and from that time gradually increases in amount until old age, being liable to special increase, particularly in females, at puberty and after the climacteric. It forms about one-twentieth of the body-weight in the adult male, and rather more in the other sex. In extreme cases of obesity one-half or even two-thirds of the total weight may consist of fat,—a negress in the United States having been recorded as weighing 850 lbs.; Daniel Lambert's maximum was 740 lbs.; whilst a bulk of 29 stone has been known in a child of eleven years, and of nearly nine stone at three years. It has been commonly noted that such enormously fat children were normal at birth, though a case is recorded of a new-born infant weighing nearly 16 lbs., and 44 lbs. at the age of eight months, no other member of the family being of unusual size.

Pathology.—The essential cause of obesity is still obscure. It is associated with certain conditions so frequently as to lead to their being considered as causes, but no one is invariably met with, and the precise determining factor remains to be found.

It prevails among certain *races* of people, whilst among others it is of rare occurrence; the inhabitants of the coldest *climates* as of the hottest are equally liable. *Age* and *sex* appear to exert but little influence, for although perhaps there is a greater tendency in

females to become stout after the climacteric, it is far from being universal, and many men put on a considerable quantity of fat after middle life, and, as already said, examples of extreme corpulence have been met with in children. Suppression of the sexual function also appears to favour obesity, as seen in castrated or spayed animals and also in many eunuchs, and women often become fat after the premature removal of both ovaries. Without doubt *heredity* strongly predisposes to the development of this state, but nevertheless its influence is often very difficult to trace, and the descendants of the excessively obese by no means always manifest the same condition. *Overfeeding*, or an excess of alcohol, particularly of malted liquors, is a well recognised associate of corpulence, and especially if this be accompanied by a lack of exercise and a sedentary occupation; yet the exceptions to this are very frequent, for many large feeders are notoriously thin, and not a few fat people maintain or even increase in weight on the most restricted dietary. Just as there are certain *diseases* which determine body wasting, so there are others which are liable to be followed by undue fat formation. Such, for instance, are simple anæmia, occurring idiopathically or subsequent to extensive hæmorrhage, the prolonged ingestion of certain mineral substances, especially arsenic, and sometimes chronic alcoholism and the occasional fatness which has been known to follow severe febrile illnesses.

A consideration of these various circumstances associated with obesity suggests their separation into those which may be presumed to produce their effect by an excessive intake of nutritive material, whilst others (*e.g.* alcohol) may be regarded as leading to over-fat formation by favouring a diminished oxidation in the process of metabolism. But even such a view of the subject is not wholly satisfactory, for since the associations are not sufficiently constant to set aside mere coincidence, there would still remain behind to be explained the essential flaw on the part of the living tissue elements. The direction in which this is to be sought for is perhaps indicated by noting that obesity is frequently connected with other forms of malnutrition, especially glycosuria and gout, these states either coexisting in the same individual or occurring alone in different members of the same family. It is in this way that the hereditary tendency particularly shows itself. Nor are indications wanting of a possible dependence of obesity upon perverted trophic nervous influence, since it occurs with considerable frequency in idiocy and other chronic mental disorders, sometimes in hysteria. Parallel with this should be remembered those extreme

cases of wasting without obvious cause, but with distinctly neurotic associations. How far the localised growth of fat tissue in certain muscular dystrophies, or in neuralgic regions, associated as these would appear to be with the condition known as *adiposis dolorosa* to be presently described, or even the symmetrical lipomata, are to be regarded as expressions of a similar nervous nutritive perversion, remains undetermined.

A difficulty which lies at the root of the proper understanding of fat formation is the want of precise knowledge of the relation of the food taken to the fat subsequently stored up in the cells of the adipose tissue. It has been proved that some of the ingested fat directly forms the body fat as such, but the greater proportion of the latter is indirectly derived from the proteids, carbohydrates, and fats of the food; that is, these substances, in the course of their digestion, absorption, and subsequent metabolic changes, are in part converted into the fat as it occurs in adipose tissue. Of these three forms of alimentary principles it is most probable that in normal circumstances the carbohydrates (partly from the fact that they constitute the larger proportion of the solids of a healthy diet) mainly contribute to the body fat. But the exact nature of this chemical change is unknown, and our ignorance on the point leaves it quite uncertain exactly how in the course of the normal metabolism of carbohydrates they are diverted into the direction which leads to the over-formation of body fat such as takes place in obesity. A similar lack of knowledge also obtains in respect to the destination of the $\overline{\text{C.H.O}}$ residue of the split-up proteid molecule, after the removal of the N compound (urea, etc.), except that its proportional composition is similar to that of fat. In the ordinary course of digestion the fats of the food are in great part decomposed into fatty acids and glycerine; the former after absorption into the columnar epithelial cells of the intestinal mucosa being reconverted into neutral fats. But inasmuch as fats form but a small proportion of a healthy diet, the share they take in the production of obesity, whether by direct or indirect transformation, must be inconsiderable.

The ultimate destination of the fats in the organism, however derived, is to become oxidised, chiefly in the muscles, into carbonic acid and water, with the production of energy in the form of heat or work. Any failure to effect the oxidation (especially by the circulation of a blood deficient in hæmoglobin and consequent deteriorated oxygen-carrying power), or an excess of fat beyond what can be oxidised, may either or both be regarded as the causes of obesity, except that the malady is not an invariable sequence of

these conditions. Moreover, there is no proof that the respiratory exchange is diminished in the obese. Upon the tissue elements themselves, therefore, must be placed the responsibility for the nutritional defect, and of the intimate nature of this nothing can be affirmed beyond that it appears to be either hereditary or acquired.

Symptoms.—The general appearance of the corpulent requires no description. Whilst some are pale and anæmic, others are of normal or even high colour. Considerable differences are exhibited in the degree of mental activity among the obese; usually indolent and lethargic, some of the hardest workers are yet to be found in their ranks; all varieties of disposition are met with, from the good-natured, happy, and easy-going, to the querulous and exacting. Similar differences exist in the range of muscular power, for although in proportion to the bulk the activity is generally diminished, yet now and then are seen individuals whose capacity for exercise is very considerable. A constant backache from overstrain of the dorsal muscles, which are dragged on by the enormous abdomen, is commonly complained of, and umbilical hernia is very usual in this condition. Many of the symptoms to a great extent depend on the interference with the functions by the presence of large masses of fat infiltrated among the tissue elements or surrounding and impeding the organs. Thus it is that the heart's action is feeble, and sometimes irregular or easily disturbed, and palpitation with dyspnoea occurring on slight exertion; the heart sounds are feeble and indistinct, and the pulse varies in accordance with the state of the individual, though generally small, quick, and compressible. A slight or even a more severe bronchitis is often met with, especially in the elderly corpulent person. There is often but little impairment of digestion, though flatulence and constipation caused by the interference with peristalsis by the fat-loaded mesenteries, or attacks of diarrhoea and offensive motions, are of frequent occurrence. Extremes of appetite are seen, but it is no unusual thing to find excessively stout people subsisting on an extremely small amount of food, though the quantity of fluid consumed is often considerable. As a rule the skin acts very freely: profuse perspirations are easily induced, and the secretion of the sebaceous glands is abundant and ill-smelling; for these reasons the creases between overhanging folds of skin in the groin and elsewhere become the seat of troublesome eczematous eruptions, which are kept up by the chafing of the opposed surfaces. Hæmorrhoids, varicocele, and other forms of varicose veins are common. Œdema of the ankles and even a

more extensive dropsy in anæmic obesity are met with, and occasionally epistaxis. The character of the urine is of course influenced by the coexistence of gout or glycosuria, and the character and quantity of the food, but nothing constant or characteristic of obesity itself has been noted. Menstruation is apt to be irregular, with a tendency to menorrhagia; the sexual appetite is lessened, and sterility is usual in both sexes, due in great measure to atrophy of the testes and obstruction of the Fallopian tubes by the pressure of intra-abdominal fat.

To a special form of obesity characterised by considerable pain and tenderness the name *adiposis dolorosa* has been given. It is a somewhat rare affection; all of the recorded cases have been women, and, with the exception of one aged twenty-two (Dr. Hale White, *Brit. Med. Jl.* Dec. 2, 1899), of middle life. A previous history of alcoholism or syphilis is generally to be obtained. In addition to a general obesity in which the face, hands, and feet do not share, there are local fatty swellings, sometimes symmetrical, sometimes irregularly distributed, but frequently situated on the arms. Pain is a marked feature, and this may precede the appearance of the lumps or even of the general obesity; it is often severe and frequently paroxysmal, and with this there is much tenderness of the localised swellings, with a general diminution of sensibility of the surface elsewhere to pain, touch, and thermal stimuli. There is muscular feebleness and a general tendency to mental dulness, with intervals of dementia or even epileptiform attacks. Among other symptoms that have been noted are headache, liability to hæmorrhages, cutaneous pigmentation, and, as in the ordinary obese patients, a tendency to bronchitis. The special interest of these cases appears to lie in their nervous associations, which have by some been regarded as of sufficient importance to warrant this condition being regarded as a distinct disease; but it appears to the writer that they might more properly be looked upon as indicating the essentially neuro-trophic nature of obesity in general, of which *adiposis dolorosa* is but a variety. In further support of this view is the observation by Dr. Dercum (by whom the state was originally described in 1892) that portions of nerve fibre removed during life showed fibrotic changes with nuclear proliferation, the adipose tissue being embryonic in character. In two cases at least the thyroid body has been found much changed and partly calcified, and it may be observed that the condition of this organ in the obese requires and would probably repay further investigation, for notwithstanding the singular exemption of the parts mainly affected

in myxœdema, there is much in this latter malady which is suggestive of its genetic relationship to obesity.

Prognosis.—Obesity is without doubt unfavourable both to longevity and good health, and it is rightly regarded as an extra risk for life assurance. Apart from the diseases with which it may coexist, the chief danger to life in this condition is cardiac failure from infiltration and degeneration of the heart muscle. The enfeebled heart favours the development of bronchitis, which in its turn reacts upon the heart, and pulmonary engorgement and œdema may be the actual cause of a fatal ending. Cerebral hæmorrhage from the giving way of an atheromatous vessel is of not infrequent occurrence. Angina pectoris, rupture of the heart, and uræmia are occasionally responsible for death, which is often preceded by some unusual exertion. The condition also determines a liability to certain maladies, especially those of a catarrhal character, and other mucous membranes than the respiratory are liable to suffer from the congestion which the general plethora and feeble heart lead to. Such subjects also bear acute diseases badly. The presence of diabetes, gout, or arterial degeneration confer their own peculiar risks and complications.

Treatment.—The problem presented in the treatment of the obese is so to regulate the nutrition as to avoid the further storage of fat and to work off by oxidation the excess which has already accumulated. The dietary therefore is the first subject of consideration, and such benefit as may follow treatment is mainly due to the observance of dietetic rules, together with the removal of the cause of the obesity so far as may be possible. Inasmuch as the body fat may be derived from each of the three groups of alimentary principles—proteids, fats, and carbohydrates—and that these substances in due proportion are essentials of a normal diet, it follows that no food can be given to the obese from which fat cannot be formed; hence the object is to give those which are less readily converted into fat, with such as may assist, in the course of their own metabolism, in the consumption of the fat already stored in the tissues. These indications are in great measure met, as shown by experience and to some extent by physiological experiment, by increasing the amount of the proteid ingesta and diminishing the quantity of carbohydrate food. For it is known that the former not only increases proteid metabolism in the tissues, but also stimulates the metabolism of non-proteids (fats and carbohydrates); and the reduction in the amount of sugars and farinaceous material in the diet removes to that extent the source from which the body fat is most readily formed.

It is these principles which underlie the various dietaries of Harvey-Banting, Certei, Ebstein, Salisbury, and others, which differ almost entirely in the relative proportions of proteid and carbohydrate foods allowed, but for the most part agree in giving relatively more of the former and less of the latter than obtains in the ordinary meals. The following table shows some of these dietaries expressed in round numbers (grammes and ounces), compared with the requirements of an average healthy adult doing moderate work; it being understood that the proteid, fatty, and carbohydrate principles are reckoned as being free from water:—

Dietary.	Proteids.	Fats.	Carbohydrates.	Fluid as Beverage.
Normal . . .	124 grms. ($4\frac{1}{2}$ oz.)	55 grms. (2 oz.)	435 grms. (16 oz.)	3-4 pts.
Harvey-Banting	170 „ (6 „)	10 „ ($\frac{1}{3}$ „)	80 „ ($2\frac{3}{4}$ „)	2 „
Certei . . .	155-180 „ (5-7 „)	25-40 „ (1-1 $\frac{1}{2}$ „)	70-100 „ (2 $\frac{1}{2}$ -3 $\frac{1}{2}$ „)	1-1 $\frac{1}{2}$ „
Ebstein . . .	100 „ (3 $\frac{1}{2}$ „)	85 „ (3 „)	50 „ (1 $\frac{3}{4}$ „)	3 „
Salisbury . .	300 „ (10 „)	5-6 „

It will be noticed that, apart from the different proportions of the various ingredients, the total amount of the ingesta is generally less than the normal, and to some extent no doubt the benefit of such a dietary to the obese is due to the actual diminution of food, though this does not apply to those who, although corpulent, ordinarily take but little.

Turning to the articles of diet which are permissible conformably to the foregoing principles, and their distribution into meals, the nitrogenous material is best taken as properly cooked, lean beef-steak or cod-fish, which contain a less proportion of fat among the muscular fibres. According to the Salisbury plan the solid food consists entirely of these articles—at least for the first week or ten days of the treatment—in quantity of 3 lbs. or more daily, equally divided between breakfast, lunch, and dinner. The ability to take and satisfactorily digest a pure meat diet is greater than is commonly supposed, and with proper precaution will do no harm even if persisted in for some time. It may be remembered that the natives of certain regions, such as the Mackenzie River district in North America, and hunters in those parts are known to subsist entirely on meat, chiefly lean, without any farinaceous food. Less advisable than those mentioned but yet permissible are mutton, game, chicken, ham, tongue, and white fish; but pork, veal, ducks, geese, salmon, and eel are to be forbidden, since they contain a large

quantity of fat and proportionately less proteid. It is preferable, but not essential, that these articles of food should be roasted or boiled.

It is difficult absolutely to exclude fat from the dietary, even from one consisting wholly of meat, but milk, cream, and butter should not be taken—at least until the weight is considerably reduced—although the few ounces taken under ordinary circumstances are not so important as fat-formers as farinaceous foods and sugar. It will be noted that Ebstein's regimen provides an excess of fat and diminution of proteids and carbohydrates. This plan is based on protecting the body proteids from waste and furnishing fats for oxidation; it takes no account of the increased metabolism of fats which is caused by proteid changes. Its object is to avoid the incidence of muscular deterioration and weakness, and to effect the disappearance of the fat gradually; such a diet, however, is apt to disgust, the fat being supplied as fat meat or butter. Whilst milk should be excluded, it may be observed that some success has been claimed for a purely skim-milk dietary, but the large bulk of liquid required makes this plan objectionable. A small quantity of cheese may be allowed.

All plans agree in reducing considerably the starch and sugar foods, especially the latter, for which saccharin may be substituted, though the withdrawal of sugar is soon tolerated. If any bread-stuff be allowed, it should be in the form of toast, rusks, or some of the specially prepared biscuits (see p. 196).

Potatoes, carrots, parsnips, peas, and beans (except French beans) are not permissible, but green vegetables and salad may be given, and fresh fruit in small quantities. The usual condiments are allowable.

Much difference of opinion has existed as regards the amount of fluid that should be taken, some, as Cœrtel, much restricting it. It is certain, however, that as the diet becomes increasingly nitrogenous, fluids should be given, and almost without limit. Many of the dietaries are certainly faulty in this respect. When only meat is being eaten it is well to diminish the quantity drunk at meals and take a pint of hot water midway between. Tea with a slice of lemon and no milk or sugar at breakfast and tea-time; plain or effervescing or Vichy water, with a little whisky or white Rhine-wine or thin claret at lunch and dinner. Beer and sweet wines are to be absolutely forbidden. Black coffee if usually taken need not be discontinued.

With regard to the dietetic treatment of obesity certain remarks

are necessary by way of caution. Thus it is undesirable to recommend it, except the individual actually exhibit symptoms due to the accumulation of fat, or whose general wellbeing is interfered with by his corpulence. Some people are very stout and yet very well; such should be left alone. It should be pursued with the greatest care, or in a modified form, by those suffering from chronic disease, or in the aged. Each case must be treated in view of age, sex, habits of life, and previous amount of food and kind thereof, and not with a blind adhesion to any one hard and fast dietary as applicable to all. It is well to commence somewhat gradually, and not suddenly to put a patient on a very restricted scale, and the weekly loss should not be allowed to exceed 3 lbs. As a preliminary it is very desirable to have the urine carefully examined and a record kept of the nitrogen excretion, and this should be repeated from time to time during the treatment; the existence of albuminuria should be a bar to any great increase in the nitrogenous food. The patient should be constantly seen during the progress of the regimen, and its details modified as occasion may require. Occasionally persons suffer distinctly in their health, and a pure meat diet is not tolerated with impunity by all, especially if the fluid intake be limited; increased arterial tension, with consequent cardiac dilatation, may follow the circulation of imperfectly oxidised nitrogenous matter. No rule can be laid down as to how much weight the patient should be allowed to lose; it depends on his original bulk and the state of health under treatment, but it is seldom advisable to pursue the regimen strictly beyond a loss of two stone, and often not to that extent. And lastly, it is to be remembered that some cases, however carefully considered may be the diet, and however faithfully carried out, will not benefit, just as there are lean individuals whom no amount of feeding on strictly physiological lines will fatten. When a sufficient reduction of weight has been effected, a greater licence may be permitted, but it is probable that sugars will require to be permanently excluded, and farinaceous foods constantly restricted in amount. The efficacy of a dietetic regimen is likely to be conditioned by other procedures, and prominent among these is exercise. The amount and kind must be regulated by the condition and circumstances of the patient; but, whilst some should be insisted on, it must on no account be such as to cause fatigue. As a beginning in extreme cases, friction, passive movements, and massage should be tried, subsequently to be followed by walking on the level. Hot baths or Turkish baths may be given with benefit—indeed a well-known

form of treatment consists of these only ; but they are not applicable when the heart power is at all deficient. A free action of the skin, and even diaphoresis, is to be encouraged. The waters of Carlsbad, Kissingen, Homburg, and Marienbad are sometimes beneficial as supplementary to the dietary. The hours of sleep should be limited, and feather beds and heavy coverlets are most undesirable.

Drugs are seldom needed, unless it be an occasional aperient, or iron in one of the more digestible forms in anæmic cases, and in these it is of distinct value ; or mineral acids with bitters when the appetite is bad and very little food is taken. Otherwise the various preparations containing alkalis, iodides, etc., are positively harmful, any diminution of weight that may follow their use being usually at the expense of the general health. Now and then benefit has certainly resulted from a course of thyroid extract, but only as a supplement to diet and massage, and it is at present impossible to forecast the cases in which this treatment will be beneficial, whilst it is certainly contra-indicated when the heart power is weak, as frequently occurs, and in such cardiac tonics may be called for.

Most of the cases of *adiposis dolorosa* have been very resistant to treatment, although temporary benefit to some has followed the regimen here indicated, supplemented by the administration of thyroid extract.

The coexistence of gout or diabetes with obesity may necessitate considerable modification of the foregoing procedure ; and the treatment of these diseases should be referred to in connection with that here set forth.

W. H. ALLCHIN.

DIABETES MELLITUS

A disorder of nutrition manifested by an increase of glucose in the blood and its excretion in the urine, and sooner or later by loss of body-weight and strength.

Etiology.—With regard to age there is a greater liability to the disease from forty to sixty (Pavy), although no age is exempt, cases having been met with as young as four and even two years. The mortality tables show a large increase for both sexes after fifteen, and the maximum for men is reached between forty-five and fifty-five, and that for women between twenty-five and thirty-five. Men are more liable than women in the proportion of three to two.

Sometimes there is evidence of direct hereditary transmission, and the disease is found associated in the family history with phthisis, diabetes insipidus, gout, exophthalmic goitre, epilepsy, and various neuroses.

A too sedentary life, good living, and the modern tendency to run the nervous system at high pressure are all conditions favouring the disease. In this connection the prevalence of the malady amongst the Hindus and Jews is noteworthy. Both lead sedentary lives, and are of nervous constitutions, and both have a liking for a diet rich in carbohydrates. On the other hand the emotionally frigid Chinese are very rarely affected. The disease is found more frequently among the dwellers of the town than those of the country, and amongst the more educated classes who work with their heads rather than their hands. The incidence too is greater with those whose pursuits are responsible and anxious, such as professional men, financiers, and engine-drivers.

Obesity and gout carry with them a greater proneness, but the cases related to both these precursors are usually of the mild type. At least one-third of the total cases show undue stoutness. That the extremes of body-weight—emaciation and obesity—should both in different cases be features of the same disease is a striking if not unique circumstance in pathology.

The *exciting causes* resemble closely those of diabetes insipidus. They comprise nervous strain, either acute or prolonged, such as severe grief or anxiety; the nervous depression produced by fevers and alcoholism; cold; blows on the head; and rarely disease of the brain. Very often no exciting cause is discoverable.

Pathology.—In health the blood and lymph contain sugar (0.12 per cent of dextrose), and in diabetes an amount definitely in excess of that found in health. From this it follows that glycosuria cannot be an error in renal excretion—it cannot be caused by the kidney excreting unduly the sugar in the blood, for if such were the case the amount of sugar in the blood would be diminished, not increased. It being granted that in diabetes there is increased sugar in the blood—hyperglycæmia—the question is, How comes it there? Before an answer to this can be attempted, it is necessary to recall the explanation given of the presence of sugar in the blood in health. According to the view usually accepted, that of Claude Bernard, the sugar of the blood is mainly derived from the glycogen which is formed in the liver out of the sugar and proteids brought by the portal vein from the intestinal tract. The liver glycogen is, as required, reconverted into sugar, and as such passes into the circulation. In the capillaries, or within the sphere of action of the bioplasm of the tissues, the sugar is broken down in some way not understood, and the supply of sugar in the blood is kept constant by a correlation between the sugar formation in the liver and the sugar destruction in the capillaries or tissues. According to this view, the sugar in healthy blood has its source in the liver.

But other authorities, Pavy amongst them, hold that sugar is present in healthy blood, not because of the liver, but in spite of it. They look upon the liver and the intestinal villi as transforming the sugar coming from the intestinal tract mainly into fat, and thus acting as barriers to its passage into the circulation. From this it follows that in health these barriers are not completely efficient, and some sugar leaks through into the blood, and in diabetes they are still more inefficient, and much sugar leaks through. Beyond the inherent improbability that the sugar in the blood in health owes its presence to an accidental imperfection of liver function, this theory has become increasingly weaker with successive investigations and has now but a narrow acceptance.

Granted then that sugar in healthy blood has its source in the liver, it will follow that an excess of sugar in the blood will be the result either of an excessive supply from the liver or a deficient destruction in the tissues. There are good reasons for thinking that both factors contribute. In hyperglycæmia, experiments show both in man and animals that the amount of glycogen in the liver is diminished—that is the liver is incapable of holding the formed glycogen. The evidence in favour of decreased sugar assimilation may be set forth as follows:—In animals glycogen can be formed

in the liver on an exclusively proteid diet, and in severe diabetes even when the carbohydrates are withdrawn from the food glycosuria persists, the glycogen then being derived from the proteid ingesta or tissues. This origin of sugar from the tissues may explain the associated emaciation. The proteid molecule is said while breaking up into urea, carbon dioxide, and water to split off a carbohydrate molecule, and from the latter the sugar is formed. Further than this it is supposed that there is a proportion between the yield of carbohydrate and that of urea, the ratio being two parts to one, so that by estimating the amount of urea in the urine in twenty-four hours we are able to judge the amount of sugar formed from a given amount of proteid. Taking the normal excretion of urea to be 500 grains per diem, 1000 grains will be the corresponding sugar formation. This amount of sugar is less than that which the healthy body is capable of assimilating, for it is known from the researches of Professor Bouchard what the sugar-consuming powers of the healthy body are, under varying conditions of age and body-weight. Yet on a starch-free diet a case of severe diabetes will excrete sugar in the urine, showing that the power of sugar destruction (glycolysis) is less than in health. Further support is lent to this view from the fact that blood, perhaps owing to the presence in it of a glycolytic ferment, possesses the power of splitting up glucose, and that in diabetes this glycolytic power is diminished.

The liver and diabetes.—It is curious that notwithstanding the close relation between the liver and sugar formation, there is no body of evidence, clinical or pathological, connecting glycosuria with any definite hepatic lesion.

The pancreas in relation to diabetes.—That the pancreas plays a part in the causation of diabetes is supported both by experiment and morbid anatomy. Complete extirpation of the pancreas in dogs is followed by diabetes. Unless the extirpation is absolute, the diabetes does not follow, not even if a mere fragment of the gland be left behind, and the pancreatic duct be ligatured. Minkowski showed further that if a bit of pancreas was successfully transplanted under the skin of the abdominal wall, and the rest of the gland within the abdomen completely extirpated, diabetes did not develop, but that if the graft was later removed too, diabetes was the result. Turning to human morbid anatomy in cases where it has been carefully examined, the pancreas has frequently (about 35 per cent) shown definite changes—such as marked atrophy, fatty and fibroid degeneration—and if the organ were examined carefully in all cases of diabetes, it is quite probable that morbid changes would be more

frequently reported. It has been suggested that these changes in the pancreas are sometimes of syphilitic origin, but though this view does not lack probability, its accuracy is not established by observation.

From these facts we must conclude that the pancreas does prevent excess of sugar in the blood, and that since a small graft out of relation to the intestinal tract, but in relation to the circulation, suffices for the purpose, this action is of the nature of an internal secretion which, thrown into the blood from the pancreatic cells, either checks sugar formation or favours sugar destruction. And further, in man, lesions of the pancreas, if sufficiently extensive, or of such a nature as to abolish glandular activity, may cause diabetes; on the other hand, there may be extensive disease of the pancreas without the slightest glycosuria.

The nervous system in relation to diabetes.—Are these derangements of pancreas and liver resulting in increased sugar formation and diminished sugar destruction in any way dependent on lesions of the nervous system? The evidence is slender. The experiment of Claude Bernard, in which puncture of the floor of the fourth ventricle was followed by glycosuria, suggests a nervous origin. In isolated cases obvious lesions, such as tumours, softening, hæmorrhage, and sclerosis, usually in the region of the fourth ventricle, have been found. On the other hand, the large majority of cases fail to show any structural changes in the nerve centres, although this does not exclude the possibility of changes unrecognisable by present methods. On the clinical side, diabetes has often followed severe emotions and mental strain, and its incidence is greater among the educated classes and those whose occupations are harassing and responsibilities great. On the whole, it may be said that the dependence of diabetes on lesions of the nervous system is fully possible, though very far from being established.

The probability is that diabetes has its origin in more than one morbid condition; in one case the liver, in another the pancreas, and in yet another the nervous system may be at fault. But the immediate cause of the excess of sugar in the blood, and the reasons for the grave defects of nutrition which accompany it, are still obscure, and will probably remain so until more light has been thrown on the nature of glycogenesis.

The urine.—This is clear, of a lemon colour, and acid reaction, with an average specific gravity of 1035-1040. The quantity is greatly increased, commonly amounting to seven or eight pints, and sometimes reaching fifteen or twenty. The night urine is less

than that of the day. Although these are the more usual features, it is important to bear in mind that in mild cases the quantity may not exceed the normal, and the specific gravity may be as low as 1015 or 1010. The normal constituents, urea, kreatinin, ammonia, phosphates, sulphates, and chlorides, are in excess.

SUGAR in the form of dextrose ($C_6H_{12}O_6$) is present, its amount varying between one and twelve per cent, and its absolute quantity from two to twenty-four ounces per diem. Except in very severe cases the amount is influenced by the presence of carbohydrates in the food, and diminished or banished by their withdrawal.

Tests for sugar—*Trommer's test*.—To a test-tube half full of urine, add rather less than half a drachm of liquor potassæ and a few drops of copper sulphate (1 per cent solution). Shake and heat the upper part of the fluid, when, if sugar is present, a yellow precipitate changing to brick-red will appear.

Fehling's test.—Boil a drachm or more of Fehling's solution (cupric sulphate, potassic hydrate, sodio-potassic tartrate, water) in a test-tube, then add the urine drop by drop. A yellow-red precipitate denotes sugar. If there is no precipitate, add urine till it is equal in volume to the Fehling; boil again for not less than half a minute, and put by to stand. If there is still no precipitate, there is no glycosuria.

The rationale of these tests is as follows: The cupric hydrate ($CuOH_2O$) which is precipitated by the action of caustic potash (KHO) on copper sulphate ($CuSO_4$) is kept in solution by sugar in Trommer's test and by a tartrate in Fehling's. On heating, however, the sugar reduces the cupric to cuprous hydrate (Cu_2OH_2O), which latter is insoluble in sugar or the tartrate, and accordingly is precipitated. The advantage of this test is that it is rapid of application, and that the solution is clear until the reducing action of the sugar forms cuprous oxide. If the urine contains albumen, this should be first got rid of by heat precipitation and filtration. In most cases either one of the preceding tests for sugar suffices, but sometimes there is doubt, and then further tests are necessary.

Charcoal filtration.—Filter the urine five or six times through animal charcoal and repeat the Fehling test. If the result is still positive, the evidence that sugar is present is much stronger, for other possible reducing agents of copper present in urine are altered by the charcoal filtration.

Picric acid test.—In one test-tube add a few drops of liquor potassæ to a saturated solution of picric acid and heat to boiling. Then add this solution to an excess of urine in another test-tube. A claret-red colour denotes sugar. The reason for heating the potash with the picric acid first is that, if the latter is impure, the solution may darken and so obscure the test.

Phenylhydrazin test.—Put in a test-tube half an inch of powdered phenylhydrazin hydrochloride and a like quantity of powdered potassic acetate. Then half fill the test-tube with urine; boil for two minutes without shaking. Allow to cool, and after some hours examine the deposit under the microscope. If sugar is present, clusters of needle-shaped crystals of phenyl glucosazone will be found.

Fermentation.—This, though the most reliable test of all, is tedious, and its use is only called for in cases of exceptional doubt.

Shake up the urine, which should be acid, and previously well boiled to drive off contained air, with a small bit of German yeast. With this yeast-impregnated urine completely fill the long limb of a Southall's ureometer (or invert a test-tube quite full over a mercury bath) and put by in a warm place for twelve hours. If sugar is present, at the end of this time there will be a bubble of gas at the top of the tube, and the density of the urine will have diminished.

Bremer's colour test.—A small quantity of a powder, consisting of three parts of gentian violet and two parts of eosin, is added to a test-tube nearly filled with urine. On gently warming the urine will turn, in the case of diabetes, a deep violet, and if normal a brownish-red colour. The striking feature of this test is that the colour reaction occurs in a diabetic even when the urine is temporarily free from sugar, and if experience should confirm its reliability it will be for this reason of great value.

Remarks on the preceding tests.—Where a copious precipitate of the typical yellow or brick-red colour quickly forms on the application of the Trommer or Fehling tests there is no doubt as to the presence of sugar. It is different when the precipitate is scanty, does not readily fall, or is of not quite typical colour. Then the reaction may be due to some other ingredient of the urine, normal or abnormal, which is capable of reducing cupric oxide. Such ingredients are kreatinin, uric acid, lactose, and glycuronic acid. The reduction of Fehling's solution which urines sometimes show after the administration of such drugs as chloroform, chloral, camphor, salol, salicylates, and benzoic acid is probably due to the presence of glycuronic acid. It is under such circumstances that the further tests are especially useful.

Quantitative test.—The estimation of sugar is made by *Fehling's solution*, 10 c.c. of which require .05 gramme of sugar to completely convert all its copper sulphate into cuprous oxide. The quantity of any given urine which will just discharge the blue colour from 10 c.c. of Fehling contains .05 gramme of sugar. From urine of the whole twenty-four hours carefully mixed, 5 c.c. is taken and diluted with 95 c.c. of water and a burette is filled with this 5 per cent solution. 10 c.c. of Fehling diluted with 40 c.c. of water are placed in a white dish under the burette, and heated to boiling point. The contents of the burette are run into the boiling Fehling in instalments, after each of which it

should be noted if the fluid in the dish is still blue ; and in order to do this, it may be necessary to temporarily remove the lamp and allow the cuprous oxide to settle. The instalments from the burette may at first be 4 or 5 c.c. at a time, but towards the end of the operation they must be quite small. When the colour is discharged from the Fehling in the dish, the number of c.c. that have been drawn from the burette is read off. For example, suppose it is 40 c.c., then 40 c.c. of diluted (5 per cent) urine or $\frac{40}{20}$ c.c. of undiluted urine contain .05 gramme of sugar. Then

1 c.c. of undiluted urine contains $\frac{.05 \times 20}{40}$ grammes of sugar. Multiply this by 100 and the percentage, viz. 2.5 per cent, is obtained, and by the number of c.c. of urine in the day the total sugar excreted in grammes is ascertained. The estimation must be carried on without delay, and the reading should be taken when the blue colour is discharged for the first time, as sometimes after standing it will return.

Pavy's method of estimation has some advantages over the foregoing. His solution, in addition to cupric sulphate, sodio-potassic tartrate, and caustic potash, contains ammonia, which keeps the cuprous oxide in solution, and thus the discharge of the blue colour is more easily seen. The ammonia being volatile, some slight modification in the apparatus is necessary. The copper solution is placed in a flask, into which passes a tube connected with the burette, the neck being lightly plugged with cotton wool. The degrees of dilution of the solution and urine are the same as in the preceding method, but be it remembered that Pavy's solution is only one-tenth as strong in copper, 10 c.c. requiring .005 gramme of sugar for their complete reduction.

The fermentation test may be employed for estimating sugar. Each degree of specific gravity lost after twenty-four hours' fermentation represents one grain of sugar per ounce of urine.

DIACETIC ACID, ACETONE, AND β -OXYBUTYRIC ACID need mention. They are all absent in the milder forms of the disease ; the first two are frequently, and the last occasionally present in the severer forms. Their presence then is a criterion of severity, whereas their absence is not evidence to the contrary. Constipation seems to favour their presence.

Test for diacetic acid.—Add liq. ferri perchlor., two or three drops at a time, to the urine ; a white precipitate of phosphates first appears, which on further addition of the reagent dissolves, and a clear Burgundy-red solution results.

Test for acetone.—Add a few drops of freshly-made concentrated solution of sodic nitro-prusside to 5 or 6 c.c. of urine, and render alkaline with liq. potassæ. A red colour results, which will soon disappear. Now add a little acetic acid, and if acetone is present a

deep red will result, whereas if acetone is absent the colour will remain yellow.

Albuminuria is not an infrequent feature of the disease. It may, however, denote a concurrent renal cirrhosis. Casts are usually abundantly present during diabetic coma.

The detection of sugar in diabetic blood is best effected by Bremer's or Williamson's tests. In Bremer's method a drop of blood is spread between cover-slips, and the latter are exposed to a temperature of about 135° C. for ten minutes. The slips are then placed in a 1 per cent solution of either Congo red or methylene blue for several minutes. The Congo red colours normal blood a bright red and diabetic blood hardly at all. Methylene blue colours normal blood violet and diabetic blood a faint greenish-yellow. Williamson's method also depends on the methylene blue reaction. These tests are of interest, and in cases where the urine is not obtainable might be a real aid to diagnosis.

Symptoms.—There are two broad types of the disease, the severe and the mild.

In the **SEVERE TYPE**, which is the form so often found in early manhood, the patient bears the impress of a wasting disease; his face is often pale, with sometimes a dull red blush on the cheeks, and the expression is listless. The existence of wasting without anæmia is very remarkable. Thirst is often the first symptom; hunger is excessive, though food brings with it but little comfort; there are polyuria and glycosuria, neither of which are removed, though they may be diminished by the exclusion of carbohydrates from the diet; the skin and hair are dry and harsh; the tongue is thinly furred but occasionally red and beefy; digestion is good considering the amount of food and drink taken; constipation is obstinate. With intervals of temporary improvement the case keeps on the down grade—the body wastes, energy and strength dwindle, complications from time to time add to the patient's distress, and after a course of from one to two or more years, death ensues, most commonly from coma or from phthisis. There are cases, on the one hand, more acute than the above, chiefly in young subjects, which run a rapid course of a few months or even weeks; and, on the other hand, those showing every gradation of diminishing acuteness towards the form next to be described.

In the **MILD TYPE** the subject is most often in the second half of life, is frequently stout, and though losing weight, does not show obvious signs of it. The symptoms above described are present in

mitigated form. By complete, or even partial withdrawal of carbohydrates, coupled with rest to body and mind, the sugar in the urine can be largely or completely banished, and the loss of flesh and strength stayed. The course is a chronic one, and with careful living, fair health may be enjoyed. On the other hand is the chance that the severe type of the disease or some complication may supervene.

In quite the mildest cases symptoms may be nearly or entirely absent, and the sugar present only intermittently, being discovered by chance or on account of some complication making its appearance.

The *onset* of diabetes often cannot be fixed with certainty. Its existence may be brought to light in several ways—excessive thirst or polyuria may be the first symptom, or perhaps wasting or weakness; or it may be underlying a case of phthisis; or a woman may seek relief for pruritus vulvæ; or the condition may be discovered during the surgical treatment of a boil or carbuncle; or again from the appearance of cataract. It may even be discovered in a proposer for insurance, who is unaware of any deviation from health.

Diabetic coma.—This expression is applied to a collection of symptoms, of which coma is most commonly a final feature, that frequently supervenes in the course of diabetes mellitus. The earlier signs are epigastric pain, lassitude and drowsiness, and, at other times, restlessness. Breathing is much increased in range, though not in frequency, is laboured and often of a sighing character, a condition described as “air hunger.” The heart is rapid and weak; the features become drawn, the extremities cold and of a leaden hue; temperature is subnormal; the breath sometimes has a peculiar ethereal smell; the bowels are, and usually have been very constipated. The urine often shows diminution both in quantity and sugar, is markedly acid, contains albumen and casts, may have a sweetish smell, and acetone, diacetic acid, and β -oxybutyric acid be present. The patient takes less and less notice of his surroundings; his apathy merges into drowsiness, and the latter deepens into coma; the circulation grows ever feebler and life ebbs away.

There are two less common forms—one in which drowsiness and later coma are accompanied by marked signs of collapse, but very little disturbance of respiration, and another in which a period of excitement and ataxia suggestive of alcoholism precedes the coma.

The symptoms end fatally in thirty-six to sixty hours, and in

some cases even more rapidly. Coma is responsible for at least half the deaths from diabetes, and it is the risk of its supervention that goes far to make the prospect of life so uncertain. It often comes on without apparent reason, though sometimes fatigue, excitement, or a too sudden change of diet will precipitate it. Constipation, and a too complete abstention from carbohydrate food in the severe type of the disease are predisposing causes.

The causation of diabetic coma is most obscure. Suggestions have been made that β -oxybutyric or diacetic acid or acetone, from the frequency with which they are present in the urine, are causally related to the condition; but these substances can be taken both by man and animals without ill result, and their presence is probably an incident rather than a cause. Some better ground for attributing the condition to β -amido-butyric acid appears to exist (Sternburg). The alkalinity of the blood in diabetic coma is considerably reduced. Symptoms resembling coma have been produced in animals by the administration of large doses of dilute acids; by the injection of glucose into the jugular vein after ligaturing the ureters, coma results in dogs (Vaughan Harley). In man the quantity of urine and sugar often diminish prior to coma, and albumen and casts appear with it. These facts suggest that failure in renal function is a causal factor, that some toxic substance, perhaps an acid, is formed by the decomposition of the sugar and failing to be excreted produces a toxæmia.

Complications.—These are extremely varied, and their occurrence is often the means whereby the existence of the disease is brought to light.

Lungs.—Phthisis occurs frequently, especially in young subjects, and one quarter if not more of the cases are thus attacked. Its features are often peculiar. The mischief may extend insidiously and quite out of proportion to the fever, cough, and expectoration. Hæmoptysis too is rare.

Gangrene of the lung is an occasional complication, and appears either as a sequel to phthisis, pneumonia, or bronchitis, or without any apparent antecedent lung mischief.

Skin.—Pruritus, which may either be general or confined to the external genitals and the skin in their neighbourhood, is common. In the latter positions the irritation is due to the growth of fungi amongst the superficial epithelial cells. The saccharine urine affords a congenial soil for these organisms, from which fact it follows that this distressing condition may be much relieved by scrupulous regard to cleanliness. The irritation of the genitals may

lead to vulvitis in women and balanitis in men, together with eczema of the skin near by. Xanthoma is described, but is rare; the eruption consists of papules with yellow tops and red edges, which vary in size from a millet-seed to a pea. Its distribution is widespread, but it is most frequent on the extremities, including the palms of the hands and soles of the feet. Pustules, boils, and less frequently carbuncles are of common occurrence. They are the immediate results of micro-organisms, to the entry and growth of which, it must be supposed, the cutaneous and subcutaneous tissues of diabetics offer but small resistance. Liability to them is diminished by keeping the skin clean and free from cracks and abrasions.

Mouth.—It is common to find the gums spongy, tender, and retracted from the teeth. The latter readily become carious, or the seat of periostitis, and they frequently become loose and even fall out. Associated often with the foregoing is aphthous stomatitis.

Blood.—Lipæmia has occasionally been observed.

Renal system.—Albuminuria is more often a feature of the chronic than the acute forms of the disease, and is especially associated with obesity, gout, and arterio-sclerosis. Its significance varies—often it is temporary and of small moment; at other times it is a sign of concurrent interstitial nephritis, a disease with which chronic diabetes is at times associated.

Arterio-sclerosis.—Diabetics of all ages show a liability to this form of degeneration, although it is more obvious with chronic forms of the disease occurring in later life. It has been suggested that instead of a complication, arterio-sclerosis may, by causing nutritive changes in the pancreas and nervous system, be a prime factor in the causation of the disease.

Sexual functions.—In males sexual desire or power or both are not infrequently diminished or lost.

Eye affections.—None of these are very common. Cataract is a late manifestation belonging to the severe type of the disease, and most prone therefore to attack young subjects. It is usually double and soft. The cause probably lies in some morbid condition of the ciliary vessels affecting the nutrition of the lens. Retinitis and retinal hæmorrhages are met with, though rarely and hardly ever in young subjects. A toxic amblyopia has also been described.

Nervous system.—Neuralgia may be severe and obstinate.

Peripheral neuritis.—This is usually of a mild type. Its favourite seat is the lower extremities. Sensory disturbances are the more prominent. They comprise numbness, cramps in the calves, and pains along the nerves and areas of anæsthesia and hyperæsthesia

varying in position and degree. Only in the severe forms of diabetic neuritis is motor power much impaired. In that case the legs are the most common seat. Sometimes the cranial nerves are affected, and of them the sixth most frequently.

The knee jerks may disappear at any stage of the illness, whether that be of the acute or chronic form. Their absence has a doubtful prognostic significance.

Such trophic disturbances as atrophy of the skin, herpes, cracking and shedding of the nails, perforating ulcers are seen from time to time. Gangrene of the lower extremities may supervene, chiefly in older subjects, and associated with neuritis or degenerate arteries.

On the mental side, beyond every degree of depression, irritability, or restlessness, we meet with melancholia, with or without suicidal tendencies, and mania; and what is very suggestive, with an outburst of mania the sugar will sometimes disappear, to return again when the mind recovers.

DIABÈTE BRONZÉ is a term suggested by Hanot to denote a rare clinical condition in which pigmentation of the skin, enlargement and cirrhosis of the liver are associated with the symptoms of diabetes. The bronzing of the skin is often the earliest manifestation; it is progressive and most marked on the face, limbs, and genital organs. The enlargement of the liver is usually smooth, there is moderate portal back pressure, and sometimes a palpable spleen. Later in the case oedema of abdomen and legs appears, there is loss of flesh and strength, and death occurs from exhaustion or from diabetic coma or other complications. Hanot regards diabète bronzé as a distinct disease; but the correctness of this view is doubtful, for more recently cases have been described (Opie and Osler) of hypertrophy and cirrhosis of the liver and progressive bronzing of the skin in other respects resembling the foregoing, but not associated with glycosuria or other symptoms of diabetes. It would appear likely from Opie's investigations that many of the cases described under the name diabète bronzé consist of a widespread pigmentation—hæmochromatosis—involving chiefly the liver, spleen, pancreas, and skin. The pigment is of ochre-yellow colour and contains iron. With the deposit of the pigment there is degeneration of the containing cells, and following this interstitial inflammation, these changes being marked in the liver and pancreas. Where the cirrhosis of the pancreas is sufficiently advanced it is suggested that diabetes results, and in more than half the recorded cases the pancreas has been observed to be pigmented and sclerosed. These investigations throw an interesting side light on the relation between

the pancreas and diabetes. It is worthy of note that all the recorded cases of so-called diabète bronzé have occurred in men.

NON-DIABETIC GLYCOSURIA

The urine of health contains a trace of sugar, but so small a one as to be unappreciable by ordinary tests. Only when the percentage of sugar reaches .05 to 1 per cent is the condition abnormal and the term glycosuria fittingly applied.

Alimentary glycosuria.—In every healthy individual there is a limit to glucose assimilation, and its excessive ingestion is followed by a slight and temporary glycosuria, the percentage of which would usually be well under .5. No such result follows the ingestion of starches, however excessive, in healthy individuals. When it does it is evidence of a deficient power of carbohydrate assimilation.

Glycosuria is met in occasional association with injuries and affections of the nervous system. Thus, fractured skull, concussion of the brain, cerebral tumours, epilepsy, all afford examples. Severe pain is sometimes a cause, as is illustrated by the appearance of sugar in the urine after a violent neuralgia or an attack of gall-stone colic; the same result may follow sudden mental anguish. It is of interest to note that animals behave similarly, the unavoidable pain attending an experiment or the fright of being tied to the table may be followed for instance by a transitory glycosuria in cats.

The urine sometimes contains a trace of sugar in cases of neurasthenia, and a knowledge of this is important to prevent a too hasty diagnosis of diabetes. A transitory glycosuria may owe its cause to specific fevers, especially influenza and malaria, though either of these may also set up true diabetes. Over-indulgence in alcohol may cause sugar to temporarily appear in the urine, as may also certain drugs, such as chloral, opium, ether, amyl nitrite, etc. The reducing action of the urine after the above drugs is sometimes due not to glucose but to the allied glycuronic acid. Occasionally sugar excretion occurs in the puerperal state, though the variety is usually lactose and only rarely glucose. Glycosuria is a common associate of both gout and obesity. Sometimes such would fall under the heading non-diabetic, but more often would denote a true diabetes.

Diagnosis.—Diabetes is a plea for the routine examination of the urine. Without it the milder forms may long escape detection, and the patient be treated for one of its symptoms or complications, such as debility, phthisis, boils, etc. If the reduction of cupric

hydrate by a drop or two of urine is prompt and definite there is small doubt as to the existence of diabetes. But if the reduction of cupric hydrate is either slight or ambiguous, the question will arise—Is sugar present? The answer to this question has already been furnished under the section on urine. If it be decided that sugar is present, though in quite small amount, the further question arises—Is the sugar caused by mild diabetes or a non-diabetic glycosuria? In the former the sugar is usually persistent on an unrestricted diet; the amount of glucose excretion is closely related to the amount of carbohydrate ingestion; and usually some symptoms such as thirst or polyuria are present, so long as the case is untreated. Whereas in the latter the sugar is both scanty and intermittent, the glucose excretion is much less influenced by the carbohydrate ingestion and no diabetic symptom is present; and further, there may be evidence of one of the pathological conditions above set forth. It must, however, be admitted that in the present state of knowledge no sharp dividing line exists between many varieties of non-diabetic glycosuria and mild diabetes. The former merges into and may lead to the latter, as is the case with mild and severe diabetes. Cases occur, especially in association with gout and obesity, which lie so near the boundary that they will be placed on either side of it according to the views of particular observers. Non-diabetic glycosuria represents vulnerability rather than disease, and who is to say where the one ends and the other begins? A more practical question is whether the term glycosuria should in practice be restricted to a narrow usage or extended to include the milder form of diabetes. Let it be admitted that these milder forms merge by every gradation into the severer and acute variety, and therefore logically, perhaps, should be styled diabetes. But clinically there is the widest difference between the young man who is rapidly losing flesh and strength and is useless for any active participation in life, and the middle-aged man who is suffering from inconvenience rather than illness, and who with care has fair prospect of enjoyment of life. If the former is called diabetes, another term is needed for the latter, if it is only to avoid the needless employment of a word which has so gloomy a significance for the lay mind.

If the patient is seen for the first time in, or bordering on, a state of coma, a diagnosis would have to be made between diabetes and other possible underlying causes, such as uræmia, cerebral lesions, alcoholism, and opium poisoning. The urine should be examined, and if necessary be drawn off by catheter. In diabetes the specific

gravity of the urine will be high and the amount of sugar large; albumen in small amount and casts will also be present, and positive results will usually be obtained with the perchloride of iron and sodic nitro-prusside reactions. In uræmia sugar will be absent and the amount of albumen often large. The Congo red and methylene blue reactions would show the presence of sugar in the blood in the case of diabetes. The association of convulsions with the coma and the presence of œdema and cardiac hypertrophy will be in favour of uræmia. Since, however, the last two are not constant features of Bright's disease, their absence does not point strongly to an opposite conclusion. Marked emaciation, deep sighing respirations, and a rapid feeble pulse are features of diabetic coma. In cerebral hæmorrhage the pulse is often slow and full, and there are signs of hemiplegia. Further the subject is not emaciated, and is often stout and plethoric. Opium poisoning would be suggested by marked contraction of the pupils. The urine, too, would be free from sugar.

Prognosis.—If on a restricted diet sugar wholly or largely disappears, and weight and strength are recovered, the case may be regarded as mild, the degree of its mildness being measured by the extent to which carbohydrate food can be tolerated without the production of glycosuria. If, on the other hand, weight and strength decline, and sugar persists in considerable amount, and diacetic acid and acetone are constantly present, notwithstanding the banishment of carbohydrate from the diet, the case is severe. The good effect of a restricted diet usually shows itself soon, if it do so at all. Considerable importance should be attached to weight and strength and their relation to the duration of the symptoms, and a too exclusive attention to the urine avoided, for be it remembered that diminution in quantity and sugar may be the accompaniments of a downward progress and the forerunners of coma. Cases associated with obesity are usually mild, provided the subjects are not young. Age is a factor of the greatest importance, the prospect in youth being much more grave. If the disease be of the severe type, and especially if the patient be young, recovery is hopeless, and the duration of life will be short. These cases are especially liable to coma and phthisis, and the former may at any time supervene with rapidly fatal result.

On the other hand, in cases of the mild type, especially if occurring in the second half of life, the prognosis is more favourable and in proportion to their mildness, provided attention be paid to the mode of living. But even in these chronic cases there is uncertainty, for

the mild form may change to the severe, or develop some serious complication. The liability to complications, however, except such as are dependent upon arterio-sclerosis, decreases with the lapse of years. Freedom from anxiety, and from the necessity of struggling for a livelihood, and the ability to carry out treatment make the outlook more hopeful. A family history of phthisis, of diabetes, or of nervous disease, is of unfavourable import.

Treatment.—Bearing in mind the relationship already shown between carbohydrates in the food and sugar in the urine, and the symptoms connected therewith, it will follow that *diet* will hold a chief place in treatment.

The first question to consider is in what measure the withdrawal of carbohydrates from the food is desirable. To answer this it is necessary to appreciate the important share carbohydrates have in supplying the body with energy. In the healthy body carbohydrates yield 3.8, fats 8.4, and proteids 3.2 calories per grm., and a calorie is the amount of heat required to raise a gramme of water 1° C. A man of average weight and energy requires about 3000 calories per diem, and this is roughly obtained as follows :—

135 grammes of proteid at 3.2 calories per grm.	. = 432
80 grammes of fat at 8.4 calories per grm.	. = 672
500 grammes of carbohydrates at 3.8 calories per grm.	= 1900
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	(Kleen.)

It will be seen, if the 500 grammes of carbohydrates yielding 1900 calories are withdrawn, what a large increase of proteid and fat will be necessary in order to meet the deficiency. In diabetics this fact is emphasised, for in them the heat value of the food is less, because of the diminished sugar destruction, and from the above figures must be subtracted the number of grammes of glucose in the urine multiplied by its heat value, which equals 3.7 calories per grm.

It is clear then that under all circumstances the removal or restriction of carbohydrates is a matter of moment, and attended with disadvantages as well as advantages. The disadvantages are the difficulty of maintaining nutritive equilibrium, and the effect on appetite and spirits of the withdrawal of some of the most cherished articles of food, especially bread. The advantage is that the hyperglycæmia in all but very severe cases is reduced, and that if this reduction is maintained for some considerable time, the tissues

regain some of their lost power of sugar assimilation and the progress of the disease is temporarily stayed. Whether there is a balance of advantage or of disadvantage in restricting the carbohydrates depends on the nature of the case. In the very severe case characterised by rapid loss of flesh and strength and a large quantity of sugar, and the constant presence of diacetic and β -oxybutyric acids in the urine, more harm than good results. The withdrawal of carbohydrates does not materially reduce the sugar, whilst it increases the weakness and distress, and may even hasten coma. In the less severe and mild cases restriction of carbohydrates is attended with advantage, but its degree and duration must both be regulated.

It cannot be too strongly insisted upon that the diminution of sugar in the urine is a means, not the end of treatment. Ultimately the value of the restricted diet in each case is to be judged by the degree of improvement in health and weight that it secures. Even in cases of moderate severity it is important to be watchful that the patient is not losing ground, notwithstanding an improvement in the urine. Much judgment is required, and in each case the laxity or strictness of the diet must be carefully weighed on its merits, bearing in mind that improvement in health and weight is the great criterion of success.

What then is the order of treatment in the moderately severe and mild cases? Begin by gradually withdrawing carbohydrates until the patient is on a rigid diet. In the mild case the sugar will quite disappear, and in the more severe type it will not, though it will diminish. Provided the general condition permits, the rigid diet should be continued for three or four weeks. By this treatment the tissues often regain some of their lost power of sugar assimilation, and glycosuria is abolished or markedly diminished. Now relax the diet cautiously; bread may be added little by little in noted quantities until sugar reappears or increases in the urine. The amount of bread, or other starch food, that can be taken short of glycosuria reappearing or increasing is a measure of the patient's tolerance, and within that limit such food is to his advantage. Even in mild cases, when quite a considerable tolerance for carbohydrates has been reacquired, it is desirable, with a view to retaining that tolerance, to prescribe at intervals of three or four months what are described as "carbohydrate fasts," lasting three or four weeks, during which a strict dietary is maintained. Except sometimes in the case of the obese or over-indulgent, it is not desirable to limit the proteid and fat ingested. The restriction of carbo-

hydrates is a trial, though a necessary one, but to add to this a strict regulation of the quantities of proteids and fats has no advantage which compensates for its liability to impair the appetite and worry the patient. Over-treatment has the further disadvantage, and this no slight one, of fixing the patient's mind on himself and his ailment.

DIETARY.—(a) Under severe restrictions this includes varieties of meat (except liver), animal soups (clear and not thickened with flour), poultry, game, fish (except shell-fish), bone marrow, butter, eggs, small quantities of efficient bread substitutes, and vegetables poor in starch may usually be added. Examples of the latter are, lettuce (2.2 per cent of starch), cucumber (2.3 per cent), asparagus (2.6 per cent), Jerusalem artichokes (1.5 per cent)—the carbohydrates of Jerusalem artichoke consist of imulin, levulose, and gum, which are assimilated relatively well—stringbeans (6.6 per cent), and spinach (3 per cent).

(b) With a diet less strict the above bread substitutes and vegetables may be allowed more freely, and to them may be added celery, mushrooms (6.8 per cent), radishes (3.8 per cent), tomatoes (4 per cent), Brussels-sprouts (6.2 per cent), and cauliflower (4.5 per cent). For fruit, strawberries (4 per cent starch), raspberries (5.3 per cent), and cranberries (1.5 per cent), orange juice (5.5 per cent), and preserved plums (2.6 per cent), cherries (3.3 per cent), and gooseberries (2 per cent), specially prepared by Blatchley. Milk, cream (3.5 per cent), cheese (2 per cent), may be employed with care. As regards milk, the lactose it contains prevents it forming part of a strict dietary. But of late a way has been found of freeing the milk from its lactose and then great advantage attends its use.¹

(c) *To be avoided*.—Vegetable and thickened animal soups, shell-fish, liver, bread, farinaceous foods (*e.g.* rice, macaroni, etc.), pastry, potatoes, and most root vegetables, peas, beans. When a small amount of potato is allowed as a concession, it should be either baked or chipped. Sugar, honey, most fruits, and especially those that are preserved.

(d) *For beverages*.—Tea, coffee, mineral waters, koumiss, and milk in moderation can be allowed. Alcohol may be taken in small quantities in the form of whisky, brandy, Bordeaux and still Moselle and Rhine wines. Of these the first two, freely diluted, are the best. The stronger wines are not advisable, and sparkling wines and most beers must be prohibited.

¹ Mr. Morris of the London Hospital has devised a method and supplies the sugar-free milk to the diabetic in-patients.

(e) *As glucose substitutes*, saccharin and saxin are invaluable. More recently lævulose has been tried, and in limited quantity can often be taken without increasing glycosuria; but its sweetening power is small.

Bread substitutes.—The greatest hardship in a restricted diet is, however, the denial of bread, and much attention has been paid to the discovery of satisfactory bread substitutes, but it cannot be said with any large measure of success. Unless bread substitutes are in great measure freed from starch they have nothing to recommend them, for they are expensive, and often unpalatable. For this reason the majority of advertised diabetic foods are irksome and costly without being efficient. They should always be tested with dilute tincture of iodine before being employed. Gluten flours fall under the above criticism, many of them containing 25 per cent starch or even more.

Protene flour makes the best *bread substitute*; it is free from starch. Protene is prepared from milk and is of moderate price. The bread, which contains a small quantity of starch, can be bought, but home-made bread and cakes are better.

The following recipes will be found satisfactory.

Pudding.—Two teaspoonfuls of protene flour: mix with a little cold milk; boil in with the rest of half-pint; add one egg beaten and two tabloids of saxin (dissolved in hot water); bake in a moderate oven. More protene flour can be used if desired.

Cakes.—Three ounces of protene flour, one ounce of butter (creamed), six small tabloids of saxin (dissolved in hot water), three ounces grated cocoa-nut, one egg and a little milk; bake in a moderate oven in small tins.

Bread.—Four ounces protene flour, one ounce ground almonds, half-teaspoonful of baking powder, and a little salt, one egg, two tablespoonfuls of milk; beat altogether well; bake in a quiet oven about twenty minutes. This bread is excellent.

Callard's brown loaf for diabetics and also biscuits by the same firm are palatable and do not contain more than 6 per cent carbohydrate.

MODE OF LIFE.—This should be as far as possible free of hard work and worry, but not of occupation and diversion. An outdoor life with suitable exercise proportional to the strength is beneficial. At the same time it is very important to avoid fatigue, strain, or over-excitement.

Woollen underclothing should be always worn, for sensitiveness to cold is great and its consequences easily become serious. Treat-

ment abroad at foreign watering-places is not to be recommended except to the quite mild cases, such as are often associated with gout and obesity. For these, resorts like Vichy and Neuenahr (alkaline), and Carlsbad, Contrexeville, and Marienbad (alkaline sulphates) are beneficial, but, as in so many other instances, the "cures" are the result far more of the change of air, scene, and occupation than the therapeutic effects of the waters.

DRUGS.—Opium and its alkaloids, morphine and codeine, are the only medicinal remedies of established efficiency. For these the diabetic has a marked tolerance, and they bring him benefit in many ways. They diminish his thirst and hunger: they diminish the polyuria, with the result that sleep is less disturbed by the necessity of micturition; they reduce his sugar, and they soothe his nerve centres. The dose should be as small as will effect the desired object. Half a grain of opium or its equivalent thrice daily is a good dose to commence with. Codeia has probably no advantage over morphia beyond the fact of its name being unfamiliar to the patient. Its dosage may begin at half a grain, and be pushed if necessary. Arsenic is useful as a tonic in diabetes, but has no specific action. Many other medicaments, such as uranium nitrate, lactic acid, salicylates, pancreatic extract, etc., have been tried without avail.

Cod-liver oil is beneficial, if the digestion will tolerate it, where there is loss of flesh.

SYMPTOMS AND COMPLICATIONS.—It is very important to guard against constipation. It is best treated with saline purgatives, either dispensed or in the form of natural waters, such as Hunyadi or Rubinat.

Pruritus vulvæ is best prevented by completely drying the parts after each act of micturition. As a local application unguent. conii is one of the best.

General itching may be relieved by sponging with Carbolic lotion (1 in 40), or Liq. carbonis detergent. (̄ss. ad oi.), or Acid. hydrocyan. dil. ʒi., glycerine ʒi., aq. ad ʒvi.—fiat lotio. The teeth should be very carefully cleaned, and if the gums are sore, a mouth wash with the following formula, Acidi carbolici liq. ʒi., glycerine ʒi., inf. rosæ acid. ad ʒiv., adding each time an equal volume of warm water, or of Borax ʒii., tinct. myrrhæ ̄ss. aq. ad ʒvi.

Thirst is alleviated by lemon juice and sipping hot water or weak tea, but not by ice.

For diabetic coma the treatment is saline transfusion. This, if

undertaken early, affords fair prospect of good results and is not hopeless even when coma is deep and the patient cold and almost devoid of pulse and respiration. If the treatment succeeds, the pulse becomes less rapid and weak—consciousness returns and the mind clears. Usually it is only a temporary rally, and after a few hours the patient relapses and dies. But very rarely the recovery from the toxæmic symptoms is permanent. Dr. T. Oliver records such a case, the patient leaving the hospital four weeks later (*Lancet*, Aug. 13, 1898). For the transfusion a .6 per cent solution of sodium chloride answers the purpose well; it should be sterilised, of the normal body temperature, and be injected steadily and not too rapidly into a vein. The injection should be about two and a half pints in volume, and may be repeated after the lapse of a few hours if necessary. If there is constipation—a usual feature—a quick purgative should be administered. A hypodermic injection of either caffeine or ether should be administered to combat the cardiac failure.

BERTRAND DAWSON.

DIABETES INSIPIDUS

The term diabetes insipidus denotes a morbid condition characterised by the persistent passage of urine excessive in quantity and very low in density, but without any constant abnormal constituent.

Etiology.—It is a rare disease, affecting all periods of life, but is less common after fifty than before. Infants sometimes develop it, and even rarely have been born with it. Males are more prone than females in the proportion of rather more than two to one. Hereditary influence plays an important part in its occurrence. It is not uncommon to find in previous generations a history of the disease itself or perhaps of glycosuria or albuminuria. Dr. Gee has recorded a striking instance of the direct transmission of the disease through four generations (*St. Bart.'s Hosp. Reports*, 1877). A history of tubercle in the family is found too often to be a mere coincidence. The influence of a syphilitic taint is more open to doubt. Among the conditions with which the malady has been frequently found associated are blows on the head, nervous strain, such as is pro-

duced by grief, anxiety, or a depressing illness, sudden exposure to cold, convalescence from acute febrile diseases, and, in the case of children, marasmus and malnutrition.

Morbid anatomy.—In some few cases disease of the brain in the region of the fourth ventricle or elsewhere has been noted, such as tumours, aneurysms, syphilitic and tuberculous growths. In one reported case an abdominal tumour, and in two cases thoracic aneurysms were found associated with diabetes insipidus. For the rest no gross changes are found after death unless they be those of some intercurrent disease, like pneumonia or phthisis, of which the patient has died. The excessive and prolonged diuresis has sometimes produced hypertrophy of the bladder, and even dilatation of the ureters and sacculation of the kidneys.

Pathology.—The usual absence of any morbid changes in the kidneys, the undoubted occasional association with some lesion in the region of the bulb, and the fact that experimental punctures of the fourth ventricle just above the "diabetic centre" will produce profuse diuresis in animals, strongly suggest a nervous origin for the disease, a view which receives support also from the nature of its clinical features and relationships. Whether the vice lies in the vaso-dilator or secretory nerve mechanisms of the kidneys we do not know. There are well-authenticated instances of transient or permanent subsidence of the symptoms resulting from an acute illness like enteric fever, a fact consistent with a nervous origin.

There are resemblances between diabetes insipidus and diabetes mellitus; their symptoms are in some respects similar; experimentally they are alike produced by puncture of the floor of the fourth ventricle and adjacent regions. In the former, traces of albumen and sugar are sometimes to be found in the urine, or there is an hereditary history of glycosuria or albuminuria.

It is an interesting question whether those subjects who are over prone to polyuria when the weather is cold or under nervous stress represent slight forms of the same disease.

Clinical characters.—The onset is sometimes sudden, the symptoms coming on in a few hours; at other times it is slow and insidious.

The urine.—This is clear, slightly acid, and very pale, with a specific gravity of 1003-1006. When freshly passed the warm urine may not register more than 1001, but if allowed to cool to the standard temperature of 60° F. the density will rise to 1004 at least. The quantity is always large, and may be immense; eight or ten pints is common, and as much as forty pints have been recorded in the

twenty-four hours. The urea excretion, with due regard to the diet, may be normal or slightly increased or diminished. As a rule the urine contains no abnormal constituent, but sometimes a trace of albumen, glucose, or inosite is present.

The thirst is unquenchable, and is the result of the excessive diuresis. If the constant desire for water is satisfied, the amount of fluid excreted corresponds roughly to the amount drunk; but if the quantity of water taken be restricted, the urine will outstrip in amount the fluid ingested, the tissues will become dehydrated, and the distress of the patient will become intolerable. The excretion of water by the skin and lungs is diminished. In some cases the general health is not affected, and the patient suffers no more than the great inconvenience of constantly imbibing and voiding fluid and the disturbance of sleep which these necessitate. Thus men have been known to follow for years even arduous callings, and women to bear children. On the other hand, it is more common for the general health sooner or later to suffer. The patient is thin and debilitated; the temperature is subnormal; he has dull aching pains in the back; he feels and looks gloomy; in temper he is irritable, and his depression is often added to by loss of sexual power; the knee jerks may disappear; the skin is dry, and sometimes itches. The appetite remains good, and may be excessive; the bowels are constipated. Hæmorrhages and white patches of degeneration in the retina have been reported.

In a later stage the appetite fails, emaciation becomes marked, and the weakness so great that the patient has to keep to bed. The skin becomes wrinkled and discoloured; the tongue red, dry, and glazed. Attacks of diarrhœa may supervene and hasten the end, or death may ensue from a low form of pneumonia or from coma. More often before this last stage of the disease is reached some intercurrent disease, such as phthisis or pneumonia, proves fatal to the patient.

Diagnosis.—This, as a rule, presents no difficulties. The polyuria associated with hysteria and hydronephrosis is intermittent, not persistent, and both these conditions have features of their own that are sufficiently characteristic. The two causes of persistent polyuria from which it has to be distinguished are diabetes mellitus and that variety of chronic nephritis in which there are no symptoms, besides a failure of health and strength, and in which the urine is abundant, and has a low specific gravity, but is devoid of albumen, or only contains a trace occasionally. But in neither of these cases is there much real difficulty. The urine of diabetes

mellitus is of high specific gravity and rich in sugar, and in granular kidney neither is there thirst, nor is the quantity of urine so excessive as in diabetes insipidus. In those cases of granular kidney in which the ordinary evidences, cardiovascular and otherwise, are present the difficulty of diagnosis does not arise.

Prognosis.—Regard must be had to the cause, mode of onset, and age of the patient. The cases that originate in organic brain disease are usually fatal. Where the cause is of recent occurrence and short duration, such, for instance, as a blow on the head or a sudden grief, the prospect of recovery is more favourable than where the cause has been in operation over a long space of time, such as prolonged anxiety. In children the prognosis is bad, and the course of the illness short. In adults a few of the less severe cases yield to treatment, but the disease is often very intractable. In the more advanced stage of the disease, when emaciation and enfeeblement are pronounced, there is no hope, and death may be expected within a few months. Attention should in all cases be paid to the daily amount of urea excreted, for, should this fall below about 300 grs., danger is to be apprehended, and death from uræmia has been known to occur in cases which post-mortem have been found associated with extensive sacculation of the kidneys and atrophy of the renal tissue.

Treatment.—The mode of life should be equable and as free as possible from stress and strain. The clothes should be warm, the food nourishing, and no attempt should be made to limit the amount of drink, in contrast with those cases where the thirst appears to be the primary cause, such as the polydypsia of hysteria. A sea voyage may be tried. Often the best medicinal treatment consists of tonics like iron, quinine, strychnine, and arsenic, the last being especially valuable.

Of specific remedies valerian, antipyrin, nitro-glycerine, and ergot are in greatest repute. Valerian may be given in the form of the tincture, beginning with ʒj., and increasing gradually to ʒss. or even more; or as valerianate of zinc (gr. ij.) in a pill thrice daily up to 15 or 20 grs. Ergot and nitro-glycerine, opposed as these drugs are in their action on the arterioles, should be given with greater caution. Unfortunately these remedies, though often doing good at first, in time lose their effect. The use of opium in this disease is not to be commended, notwithstanding that benefit has been stated to follow its administration; its use is perilous and even has been fatal.

PHOSPHATURIA—OXALURIA

The urine being one of the chief channels for the excretion of tissue waste, might be expected to furnish evidence of the perverted metabolism which characterises the different forms of malnutrition. So far as sugar, urea, and uric acid are concerned this is the case, but as regards other waste products the information obtained from the examination of the urine is not so reliable in demonstrating the connection between various states of ill-health and the presence of abnormal substances or alterations in the amount of normal constituents. This is in part owing to want of precise knowledge of the chemistry of tissue metabolism, and of the exact relationship of the urinary excreta to tissue activity, and also to the fact that many of the decomposition processes which go on in the intestine, bacterial and other, lead to the formation of substances which are absorbed into the system and excreted in the urine, and are not in the proper sense products of tissue interchange. The presence of such bodies renders uncertain the analysis of the urine from the standpoint of the source of its constituents and the clinical interpretation that is to be put upon their presence. Another cause of difficulty in properly estimating the significance of the urinary solids lies in the circumstance that the amounts of many of them are liable to be influenced by conditions quite apart from the nature and activity of tissue metabolism, such, for instance, as the degree of acidity of the urine, the composition of the ingesta, and the perfection or otherwise of the entire digestive function. Hence it is that an excess of a substance in the urine may be more apparent than real. A few of the more defined conditions may be mentioned here, but owing to their frequent association with dyspepsia, a fuller reference to them will be made elsewhere.

PHOSPHATURIA.—Although most of the urinary phosphates are directly derived from the food, a certain amount results from the oxidation of such tissue constituents as nuclein and lecithin. Setting aside the accidental and apparent excess of phosphates in the urine, due to diminished acidity of the latter from any cause, cases are met with in which the total quantity of the earthy phosphates is so constantly increased as perceptibly to raise the specific gravity of the urine, or if this be alkaline, to cause a deposit in which stellar crystals of the lime salt are to be found, a condition which has been termed "phosphatic diabetes." Such an urine is found to be associated with fairly well-marked clinical features,

such as emaciation, nervous irritability, and dyspepsia, with constant pain in the back and loins, and a general state of ill-health that may usher in phthisis or fatal diabetes. What may be the starting-point of this symptom-complex is difficult to say, and equally uncertain is the relationship of the phosphatic excess to the other phenomena. The treatment of the condition appears to be best effected at first by opium, which diminishes tissue waste, and later by general tonics and careful feeding.

OXALURIA.—The normal amount of oxalate of lime daily excreted averages .01 to .02 grm., which is held in solution by the acid phosphate of soda, and is probably derived from the food. An excess, when not due to ingesta (rhubarb, cabbage, etc.) or to imperfect digestion, may be derived from nucleo-proteid metabolism, or, as seems possible, from the incomplete oxidation of carbohydrates, since there is a marked tendency to oxalate excess in diabetes, the over-excretion of the salt sometimes occurring with a temporary diminution of the sugar. It is significant that an increase in the uric acid excretion commonly accompanies that of the oxalate. Symptoms not unlike those of phosphaturia are found in connection with a constant oxaluria, prominent among them being a mental irritability, varied by depression amounting to hypochondriasis, indigestion, and general debility. But how far these very evident signs of malnutrition are to be associated with a primary perversion of tissue metabolism, or are the result of an original fault in digestion, or what bearing the excessive oxalate excretion has is quite unknown. Treatment, so far as it is called for, should be directed towards the digestion, both by regulated diet and by such aids to the process as mineral acids.

Of such rare conditions as **CYSTINURIA** and **ALKAPTONURIA** little is really known. The former, recognised by the occurrence in the urine of the characteristic hexagonal crystals, is probably in most cases the expression of intestinal putrefaction, although its occasional occurrence in several members of the same family suggests an origin in tissue metabolism. No constant symptoms appear to be associated with its appearance.

The condition known as **alkaptonuria** appears to be due to the presence of homogentisinic acid, which is almost certainly derived from tyrosin, probably by microbic action in the intestine. "The urine of alkaptonuric individuals darkens rapidly after it is passed, acquiring a deep brown colour. It reduces Fehling's solution on

heating, and this may cause the condition to be mistaken for glycosuria. Alkaptonuria is usually congenital and life-long, and is apparently without injurious influence upon the health of the individual. The great majority of patients are males, and a considerable number of the congenital cases have occurred in brothers and sisters. A temporary alkaptonuria has been observed in a few instances." (See paper, with bibliography, by Dr. A. E. Garrod, *Tr. R. Med. Chi. Soc.* 1899.)

W. H. ALLCHIN.

GOUT

Gout is the manifestation of a number of morbid tendencies, some of which may be inherited and some acquired, which result in different conditions associated with the arthritic diathesis. If the joints become affected, articular or regular gout results ; if other organs or tissues become affected, then the term irregular gout is applied.

Pathology—Gout is associated with the presence in the blood of an excess of uric acid in combination with sodium. Uric acid $\text{H}_2(\text{C}_5\text{H}_2\text{N}_4\text{O}_3)$ is a bibasic acid, and forms the following three classes of salts :—(1) the *neutral urates*, such as $\text{Na}_2(\text{C}_5\text{H}_2\text{N}_4\text{O}_3)$, the neutral sodium urate ; (2) the *biurates*, such as $\text{NaH}(\text{C}_5\text{H}_2\text{N}_4\text{O}_3)$, the sodium biurate ; and (3) the *quadriurates*, such as $\text{NaH}(\text{C}_5\text{H}_2\text{N}_4\text{O}_3)$, $\text{H}_2(\text{C}_5\text{H}_2\text{N}_4\text{O}_3)$, the sodium quadriurate. Of these three classes of salts the neutral urates cannot exist in the living organism, and therefore take no part in the pathology of gout. It should also be borne in mind that uric acid does not and cannot exist in the blood in the free state. Sodium quadriurate is the soluble uric acid compound which is originally present in the blood of gouty subjects. This salt is, however, an unstable body, and after a certain time it unites with some of the sodium carbonate of the blood to form the stable but much less soluble sodium biurate. If this biurate is produced in larger quantities than the fluids of the body can retain in solution, it becomes precipitated in various structures in the crystalline form, and then constitutes the gouty deposit, and the only deposit that occurs in gout.

Different views have been held at various times as to the causation of gout. That which regards gout as the result of a true toxic action exerted by the uric acid salt dissolved in the blood is untenable for these reasons :—(1) there is no experimental proof that uric acid is a poison ; (2) a gouty subject just prior to the advent of an attack of acute gout shows no signs of poisoning, although the fluids of his body are then saturated with a salt of uric acid ; and (3) in certain blood disorders, such as leucocythæmia and severe anæmia, the blood is frequently highly charged with a salt of uric acid without the production of any toxic symptoms that could be referred to that substance. Again, the various suggestions as to the uric acid being merely a

by-product in the gouty process quite fail to explain many of the phenomena of gout. The remaining view that the uric acid salt only exerts a baneful effect after precipitation from the blood and deposition in the tissues appears to be the most tenable one. This theory regards the soluble uric acid salt as being destitute of poisonous qualities and as producing no harmful results so long as it remains dissolved in the fluids of the body. When, however, the fluids become over-saturated with this compound, a crystalline deposition of sodium biurate occurs which then acts as a mechanical irritant to the tissues and structures in which the deposition takes place.

The source of uric acid.—The overcharging of the blood in gout with a salt of uric acid must be due to one or more of the following causes:—(1) production of uric acid in the normal manner, but insufficient excretion of it; in healthy individuals uric acid is always formed in certain quantities, but is completely excreted; (2) over-production of uric acid while the excretion remains about normal; and (3) diminished destruction of uric acid by imperfect oxidation or by some other means. The two last-mentioned views are untenable; for with regard to the last there is no proof that the process of oxidation or any other process going on within the organism destroys uric acid, and the second is based on the erroneous assumption that the kidneys can only eliminate a certain amount of uric acid, whereas there is abundant proof that an increased production of uric acid does not lead to gout so long as the kidneys remain in a normal condition. We are therefore restricted to the explanation of the cause of the presence of the salt of uric acid in the blood in gout being due to the production of uric acid at the normal seat or seats of its manufacture, and to its subsequent imperfect excretion. That a deficient excretion of uric acid occurs in gout has been shown by recent accurate estimations of the elimination of uric acid in gouty subjects.

The question next arises whether the uric acid salts, which in gout are imperfectly excreted, are manufactured in the organs and tissues of the body generally and thence passed into the general circulation, or whether they are produced only in the kidneys, and then, in consequence of imperfect excretion by these organs, the residual quantities of uric acid salts are absorbed from them into the general circulation. Now if uric acid be produced as such or in the form of salts in the liver or spleen or tissues generally, then it follows that it must be conveyed in the blood to the kidneys in order to be excreted, and if this be the case it ought to be capable

of detection in the blood of healthy individuals, and of healthy animals that excrete uric acid. Careful examination of the blood of healthy human beings and of various mammals has however always failed to reveal the presence of uric acid, though urea is always present in such blood. This evidence suggests that since uric acid salts are not conveyed in the blood to the kidneys they must be manufactured in those organs, and this view of the renal formation of uric acid is supported by the fact that although birds excrete the whole of their urinary nitrogen in the form of uric acid and not at all in the form of urea, yet the blood of birds always contains an abundance of urea, and only very minute amounts of, or no uric acid salts. This evidence that the blood of birds always contains urea, but little or no uric acid salts, whilst the urinary excrement of birds contains no urea, but consists entirely of compounds of uric acid, can only be explained by the view that the uric acid is manufactured, at all events to some extent, in the kidneys, and that the urea brought to the kidneys by the blood is the antecedent, or one of the antecedents, out of which the kidneys manufacture that uric acid.

The renal origin of gout.—It would therefore appear that the first step in the pathogenesis of gout is a failure on the part of the kidneys—from transient or permanent mischief—to perfectly excrete the uric acid salts formed in them, and that consequently absorption of the non-excreted portion takes place from them into the general circulation, where the uric acid exists at first as sodium quadriurate, and so forms the source from which the gouty deposit is derived. It is probable that some affection of the kidneys always precedes any gouty manifestations, and that this possibly transient affection may subside if the exciting cause of it be removed, or it may pass on to an obvious structural lesion. It may be that this renal vulnerability constitutes the hereditary factor of gout. The affection may also be started by various causes, such as excessive indulgence in nitrogenous foods, wines, and beers, the toxic effect of lead, and the influence of nervous impulses, such as mental shocks, severe accidents, etc. The anatomical seat of the kidney affection is apparently in the epithelium of the convoluted tubes, whilst the increase of interstitial tissue is most likely a secondary change. Possibly the organic changes in the kidneys are not necessarily the same as those in other kidney affections where the same tissues are involved; in other words, there are, doubtless, organic changes in the epithelium of the convoluted tubes and in the interstitial tissue which do not lead up to or cause gout.

Uric acid is probably formed wholly or in greater part in the kidneys by the combination of urea ($\text{CH}_4\text{N}_2\text{O}$) with glycocine ($\text{CH}_2\text{NH}_2\text{COOH}$) or with one of the derivatives of the latter body conveyed from the liver. This view is supported by the fact that uric acid can be made artificially by the union of urea with glycocine, and also by the well-known fact that amongst the carnivora whose urine contains little or no uric acid, the bile contains no glycocholic but only taurocholic acid, and therefore yields no glycocine.

Formation and seats of gouty deposits.—As previously mentioned, the unstable sodium quadriurate circulating in the blood of gouty subjects becomes converted after a variable period of time into the much less soluble sodium biurate, which then deposits in such tissues as, either on account of having received previous slight injuries, or because of their poor vascular supply and the sluggish movement of fluids in them, specially favour its deposition. These tissues belong to the connective-tissue class—cartilages, ligaments, tendons, and the cutaneous and subcutaneous connective-tissues. It is quite possible that nervous influence may accelerate this deposition of biurate. It is well known that whatever depresses the nervous system, such as great fatigue, rage, fright, worry, or excitement, may cause an attack of gout in a gouty subject. This is probably due to nervous influences depressing the excretory power of the kidneys for uric acid salts, and so leading to an increased absorption of quadriurate into the general circulation. The great toe-joints and the ears are the commonest seats of the gouty deposit. The reasons for the selection of the toe-joints are the liability of the joint to injury from having to support the weight of the body, and from being subjected to sudden shocks; the remoteness of the joint from the heart, so that the force of the circulation is at its minimum at that part; and the poor vascularity of the tissues of the joint. In the helix of the ear the sluggish circulation and the coldness of the organ may account for the frequency with which uratic deposits are found in that situation.

Cause of the inflammation accompanying the gouty paroxysm.—The gouty paroxysm is due to precipitation in the crystalline form of sodium biurate, the crystals being distributed throughout the implicated tissue in the form of delicate needles, aggregated into tufts, bundles, and stars. When deposition occurs in cartilage the crystalline deposit acts as an irritant and causes inflammation, leading to proliferation and necrosis of cartilage cells, which may be followed by erosion of cartilage and of uratic deposits and consequent displacement of the

latter into the cavity of the joint. Although the inflammatory part of an acute gouty attack is secondary to the deposition of sodium biurate crystals, it seems to be necessary that such deposition should occur fairly copiously and suddenly in order to start the inflammatory process. Undoubtedly, as in cases of chronic gout, the biurate may deposit slowly and quietly in joints without the development of any acute attack.

Post-mortem appearances.—A *joint* opened in the acute stage of gout shows inflammation, swelling of the various fibrous structures, and effusion into the cavity of the joint. The gouty deposit may be fairly uniformly distributed over the cartilage, or it may occur in small areas as specks, streaks, or patches. It is deposited first in the articular cartilages, but afterwards involves the various fibrous structures of the joint. The deposit is not on the surface, but is situated interstitially in the substance of the cartilage, and is densest close under the surface, becoming thinner towards the deeper parts. The layers of cartilage near the bone are quite free from deposits. The synovial fluid may contain crystals of sodium biurate. The deposit may infiltrate all the tissues outside and around a joint, and may extend towards the surface, forming the so-called chalk stones.

The form of *kidney* affection especially met with in cases of gout is that of the granular form, with atrophy of the organ. Deposits of sodium biurate may be found in the intertubular tissue, and in the region of the papillæ in a small proportion of the cases.

Etiology—*Age*.—Gout is mainly a disease of middle and late life, but it may become manifest earlier if there is a marked hereditary tendency.

Sex.—Gout most commonly occurs among males, due no doubt to the habits of men being more conducive to its development than the more temperate habits of life of most women.

Hereditary predisposition.—This is the most important factor in the determination of gout. The females of gouty families frequently escape the apparent development of gout in themselves, yet transmit the liability to the disease to their children. It is doubtful, however, whether true atavism occurs in connection with gout, that is, whether gout entirely misses a generation. It is more probable that it appears in some form, irregular or otherwise, in the generation that it is supposed to have passed over.

Habits of life.—Excessive indulgence in alcohol, especially in the form of wines and beers, and excessive consumption of nitrogenous and rich foods, are powerful factors in the development of gout.

Indolent habits and inadequate physical exercise also strongly predispose to gout.

Lead poisoning.—Chronic lead poisoning predisposes to gout, probably by affecting the kidneys, and so interfering with the proper elimination of uric acid.

Immediate exciting cause.—An attack of acute gout is frequently induced by unusual indulgence in food or drink, or by some powerful emotion, such as a fit of anger, worry, or anxiety, or by exposure to cold, or by the receipt of some injury. For the production of gout, whether of the regular (articular) or irregular (abarticular) type, the deposition of sodium biurate in the organ or tissue affected is essential. The mere presence of uric acid in the blood in the form of dissolved sodium salts is insufficient for the production of any form of gout, in the absence of deposition of the biurate from the fluids of the body.

THE FORMS OF GOUT AND THEIR CLINICAL FEATURES

ACUTE GOUT.—Twinges of pain in some of the joints may occasionally precede the acute attack, but, as a rule, no warning ushers in the first attack of gout. Subsequent attacks may be preceded by pain in the feet or by cramps, dyspepsia, constipation, mental depression, or loss of appetite. The seizure most frequently occurs in the early hours of the morning, when the patient is awakened by severe pain, generally in the right great toe. The pain increases in intensity, but, after some hours, partial abatement, accompanied by a gentle perspiration, occurs. In the morning the toe is swollen, the skin is tense, shiny, of a purplish red-brown, and extremely tender, and the veins are distended. During the second night the severity of the pain may recur, and such recurrence may, in the absence of suitable treatment, take place for many days. The pain in the joint is excruciating, and is quite out of proportion to the external signs of inflammation. As the attack subsides the swelling and redness of the affected part lessen, the skin itches and pits on pressure, and desquamation follows. The œdema around the joint is characteristic, and is useful in distinguishing the affection from rheumatism. Gouty inflammation of a joint is not followed by suppuration. The temperature most commonly ranges from 99° to 102° F., and the attack is generally accompanied by thirst, anorexia, and constipation, whilst the urine is scanty, high coloured, and usually deposits amorphous urates on cooling. Temporary albuminuria has been frequently observed during the early stages of

the paroxysm, and occasionally slight albuminuria persists throughout the attack. An attack of acute gout lasts on an average from eight to fourteen days in persons of strong constitution, but with advancing age the duration becomes prolonged. After an attack of acute gout a patient frequently feels much better in health than before the attack. A first attack of gout may not be followed by another, provided attention be paid to diet and the general mode of life. On the other hand frequent recurrences may occur. The majority of first attacks of gout occur in the great toe-joint, but the disease may start in the ankles, instep, knee, small hand-joints, elbows, and very occasionally in the shoulders and hips. The selection of any particular joint for a primary attack is probably dependent on slight inflammatory or trophic changes in that joint from some recent injury or strain.

CHRONIC GOUT.—As the recurrence of gout becomes more frequent more joints are affected, and the attacks also become more prolonged unless efficacious treatment is resorted to. Tophi are apt to form in various localities, and so give rise to the so-called *tophaceous gout*. These tophi consist mainly of deposits of sodium biurate under the skin, and are principally found in the auricles of the ears, in the vicinity of joints, and in the bursæ over joints. If excessive accumulation of the biurate occurs, these tophi assume a great size and may then cause the integument to give way, when a discharge of a thick creamy fluid containing an abundance of crystals of sodium biurate takes place. The swelling in the vicinity of a joint may give rise to fluctuation, but such swelling should never be opened. Considerable enlargement and deformity of joints may occur in connection with chronic gout to which the deposits of sodium biurate only contribute in small part. In such cases the enlargement is due to thickening of the synovial membrane, and to overgrowth of the cartilages and of the ends of the bones and surrounding fibrous tissues. This form constitutes the so-called *chronic deforming gout*. Permanent deformity of the affected joints may result, and partial dislocations and ankyloses may also occur. On the other hand the uratic deposits may undergo complete solution, and the joint be left in an apparently normal condition. The urine of chronic gout is somewhat increased in quantity, and is of lower specific gravity and somewhat paler than normal. The amount of uric acid eliminated is diminished. A trace of albumen is frequently present, and permanent albuminuria is a fairly common occurrence in confirmed gout. Before an attack of gout the output of uric acid is low, and it is also diminished in the early part of the

attack. The excretion of phosphoric acid in the urine is stated to correspond very closely to that of uric acid, being low before and during the early part of the paroxysm, but rising as the attack passes off. Oxaluria is of fairly common occurrence in connection with gouty attacks. The most reliable process for the estimation of uric acid in the urine is the Gowland-Hopkins method. This process depends upon the fact that when urine is saturated with ammonium chloride, all the uric acid is precipitated as an ammonium urate. From the ammonium urate the uric acid is set free by means of hydrochloric acid, and the amount of it is subsequently determined by titration with a standard solution of potassium permanganate.

Changes in the heart and circulation, consequent on gouty affections of the kidneys, are indicated by hypertrophy of the left ventricle, a strong cardiac impulse, displacement of the apex beat to the left, and accentuation of the aortic second sound. The pulse is of high tension, and the arteries are hard, tortuous, and sometimes atheromatous. Under such conditions a cerebral hæmorrhage may occur. Attacks of true angina pectoris, associated with arterial degeneration and softening of the walls of the heart, occasionally occur in gouty subjects.

SATURNINE OR LEAD GOUT.—Chronic lead poisoning gives rise to both chronic kidney disease and gout. The liability of those suffering from chronic plumbism to be attacked by gout is probably due to the action of lead salts on the renal epithelium causing a diminution in the excretion of uric acid, so that an absorption of the non-excreted portion takes place from the kidneys into the general circulation. The patient suffering from saturnine gout, unlike the majority of sufferers from inherited gout, is pale, thin, and anæmic. If the lead poisoning has been of short duration, the lesions may yield to treatment, but after a prolonged absorption of lead into the system, the kidney condition is generally incurable.

IRREGULAR GOUT.—Gout appearing in a situation other than a joint is regarded as irregular or abarticular. Irregular gout may accompany arthritic gout, or may take its place, or may alternate with it, but more frequently it occurs among those who have never suffered from gout in the joints, but who are predisposed to gout either by inheritance or by mode of life. The most important points to attend to in the diagnosis of irregular gout are the question of heredity, the habits of the patient, the nature of the attack, a careful examination of the urine and, if possible, of the blood or

blood serum, and, lastly, the successful reaction to therapeutic remedies. Cramps and aching pains in various muscles, and tingling sensations in the hands and feet, are frequently associated with irregular gout. Probably all forms of irregular gout are due to the precipitation in the crystalline form of sodium biurate in the organ or tissue affected. Deposits of sodium biurate have been found after death in the valves of the heart, in the walls of arteries and veins, in the vocal cords, in the mucous follicles of the pharynx, in the walls of the bronchial tubes, in the meninges of the brain and spinal cord, in the spinal nerve-sheaths, in the sclerotic coat of the eye, and in the fibrous envelope of the retina. Irregular gout may affect (*a*) the alimentary tract, causing pharyngitis, œsophagismus, dyspepsia, or gastro-intestinal catarrh; (*b*) the air-passages and lungs, causing laryngitis, tracheitis, bronchitis, or asthma; (*c*) the heart and vessels, causing cardiac irritability, anginal attacks, or phlebitis; (*d*) the nervous system, causing migraine, neuralgia, neuritis, or mental depression; (*e*) the genito-urinary system, causing gouty kidney, uric acid gravel, or urethritis; (*f*) the skin, causing eczema, herpes, pruritus, or urticaria; and (*g*) the eye, causing gouty inflammation of any of the structures of the eye—conjunctivitis and iritis are the two commonest eye affections caused by the gouty condition. Irregular gout may also manifest itself as glycosuria or diabetes. The glycosuria is in all probability frequently hepatic in its origin. Glycosuria is generally associated with some form of irregular gout, and but seldom with the ordinary articular gout, but very occasionally it alternates with true gouty attacks, and then, while the glycosuria lasts the patient is quite free from articular gout, and *vice versâ*. The glycosuria may at first be very slight, but if not checked by proper dietetic treatment it may lapse into true diabetes. With regard to the prognosis in gouty diabetes, much depends on the manner in which the affection responds to dietetic treatment. If the sugar in the urine quickly disappear, and if several months elapse before its re-appearance, then the prognosis is fairly good, and life may continue for many years.

RETROCEDENT OR METASTATIC GOUT.—This form of gout occurs when a sudden subsidence of the inflammation in a gouty joint is succeeded by the development of the disease in one or more of the internal organs, such as the stomach, intestines, heart, or liver. Such attacks frequently follow an exposure to cold while suffering from an articular attack, and especially after indiscretion in diet. If the attacks rapidly shift their position the affection is termed *flying gout*. Attacks of retrocedent gout have not un-

commonly followed the baneful practice of suddenly plunging a gouty foot into cold water. It is quite possible that the attacks are caused by a deposition of the crystalline sodium biurate in the affected viscus, and that this crystalline biurate acts as a mechanical irritant, and so produces inflammation of the organ. On the other hand, the attacks may simply be of nervous reflex origin, due to vaso-motor disturbance producing a condition of hyperæmia or congestion of the affected viscus. The following are the principal forms of retrocedent gout, with the symptoms indicative of the sudden transference of the attack to the affected viscus.

Retrocedent gout of the stomach.—The symptoms consist of severe pain in the stomach, accompanied usually by vomiting and a feeling of general oppression, depression, and faintness. Palpitation may occur.

Retrocedent gout of the intestines.—The usual symptoms are severe abdominal pain, vomiting, tympanites, and constipation.

Retrocedent gout of the heart.—The symptoms are severe palpitation, pain in the region of the heart, a sensation of constriction of the chest, dyspnœa, a small, feeble pulse, and great anxiety. Syncope attacks may occur.

Retrocedent gout of the brain.—Apoplexy is the most frequent symptom. Congestion of the brain or meninges may occur, and may be followed by headache, stupor, convulsions, delirium, and occasionally by maniacal attacks. Transient attacks of aphasia, amnesia, and hemiplegia sometimes occur, and are probably due to congestion of the brain.

Diagnosis.—Gout, both in its acute and chronic form, requires to be distinguished from certain other arthritic affections. The former from acute rheumatic arthritis, acute synovitis, or joint inflammation of pyæmic origin; the latter from rheumatoid arthritis, chronic rheumatism, gonorrhœal arthritis, or chronic synovitis due to trauma.

As a general diagnostic measure the blood may be examined for uric acid liberated from its salts, by the following method, known as Garrod's thread test:—about two drachms of the serum furnished by the blood on standing, or of the fluid raised by a blister, are placed in a large watch-glass, acidulated with acetic acid and a fibre from a piece of linen immersed in the fluid. The watch-glass is then covered over and left in a warm room. When, by evaporation, the serum has been brought to the consistence of a thin jelly, the fibre, still on the watch-glass, is to be examined under a low power of the microscope, when it will be found to be studded

with crystals of uric acid in the case of serum obtained from a gouty subject.

The distinction of acute arthritic gout from acute arthritic rheumatism should not be difficult. The sudden onset usually in one joint, and that the great toe, and its limitation to that situation, contrast strongly with the successive invasion of several of the larger articulations which is commonly the case in acute rheumatism. Not less striking are the appearances presented by the affected region. In place of the somewhat swollen and slightly reddened surface, which is tender and painful in the latter disease, the purplish, shiny, tense, and moderately swollen joint, over which course distended veins and covered with a gentle perspiration, excruciatingly painful and intolerant of touch, undoubtedly proclaim gout. The constant association of endocarditis or some other of the rheumatic manifestations, either previously or concurrently, may help the diagnosis should that be in doubt, and the history of previous attacks and their course would also assist.

It is seldom that any difficulty would occur in distinguishing acute articular gout from acute synovitis due to trauma or a pyæmic inflammation of the joints. The history of the case and of accident, or the presence of other signs of a septicæmia, are usually all-sufficient.

Some hesitation may occur as to the diagnosis of chronic articular gout from other chronic joint affections, and this is in some measure due to want of clear agreement as to what constitutes the essential characters of some of these conditions, and their exact limitations as clinical entities. The conditions commonly confused with gout is that known as osteo-arthritis or rheumatoid arthritis, or most improperly called "rheumatic gout." The character of the chronic gouty joint, with more or less uratic deposit, has been described, and though there may be much deformity it differs in appearance from that met with in the other malady where lipping of the cartilages and osteophytic outgrowths are diagnostic. Moreover, the hands are usually first and chiefly affected in osteo-arthritis rather than the feet as in gout, and more often develops in women rather than in men, and especially as a result of exhaustion, worry, or other causes of general malnutrition, which are rarely the antecedent conditions of gout. Although, as will be described, osteo-arthritis may occur acutely, it more often begins insidiously and without much pain. Its distribution is far more symmetrical than that of gout, and there are also other phenomena suggestive of its neurotic relationship, such as muscular wasting, glossy skin, and

even neuritis, whilst the permanent deformity of the hands is characterised by an ulnar deflection of the fingers, Heberden's nodes, etc. The occasional involvement of the maxillary articulation is characteristic.

Inasmuch as what is really meant by "chronic rheumatism" is still uncertain, it may well be that confusion may exist between this and chronic gout. The existence of uratic deposits in the joints, if they can be detected, or of biurates in the blood, should clear up the diagnosis, which is helped by the history of the onset and early progress of the case.

The history also is an important consideration in distinguishing chronic gout from a gonorrhœal synovitis in which the joint is liable to early fixation by fibrous adhesions.

As an assistance in the diagnosis of a chronic articular affection, there is a rough but fairly sure test to be found in the benefit which almost invariably follows the administration of salicylate of soda in the true rheumatic affection, whilst it causes but little improvement in gout or in osteo-arthritis.

It is not common to find rheumatoid arthritis and gout associated in the same patient. What occasionally does occur is that gouty deposits may form in joints suffering from rheumatoid arthritis, but it is more in the nature of an accident than anything else. A person suffering from rheumatoid arthritis who indulges in rich living for a lengthened period of time, and especially if he takes much wine, may develop gout, and so gouty deposits in the joints of a patient suffering from rheumatoid arthritis may occasionally be met with. Still it is only a complication, there is no actual relationship between the two conditions, and one does not predispose to the other. Rheumatism certainly predisposes to rheumatoid arthritis, because a person who has been subject to rheumatism has the nutrition of the joints so much impaired for the time, that if there is any opportunity for the specific micro-organisms to gain access to those joints, it is very likely that they will there develop and flourish. That is why cases of rheumatism and rheumatoid arthritis do occasionally go together.

Prognosis.—If no complications arise, if the attacks are not too frequent, and if no serious amount of albuminuria occurs, the disease is not likely to materially shorten life, especially if the patient is amenable to proper treatment and discipline. The prognosis in cases of irregular gout affecting the heart, and in cases of retrocedent gout is much graver.

Treatment.—No routine treatment can be adopted which is

suitable to all cases. The treatment of individual cases must be regulated according to the nutritional condition of the patient, his habits, surroundings, and mode of life. It should have for its aim the following objects :—(1) the treatment of the gouty paroxysms, and the relief of the pain as speedily as possible ; (2) the treatment of the subacute or chronic condition and the prevention of the recurrence of an attack, which may be effected by the promotion of the elimination of uric acid, by checking any excessive formation of uric acid that occurs in some subjects, and by careful attention to diet and general hygiene ; and (3) the treatment of the affected joint or joints, with the object of removing the uratic deposits, and of preventing permanent deformity.

A careful examination of the urine should always be made, and it is especially important to ascertain whether the kidney affection is in the functional or organic stage. The indications that the gouty affection of the kidneys is passing from the functional into the organic condition are the existence of a certain amount of polyuria, a low specific gravity of the urine—usually from 1007 to 1016—the presence of a small quantity of albumen and of a few granular casts, if a careful microscopical examination is made after centrifuging the urine, and a diminished daily excretion of uric acid and generally of urea. It is desirable before commencing treatment, and from time to time during treatment, to ascertain the amount of uric acid that is being daily eliminated in proportion to the body-weight of the patient. This determination must be made on a sample of the mixed urines of twenty-four hours, as the mere determination of the percentage of uric acid in a casual sample of urine constitutes no guide to the actual amount that is being daily excreted.

Treatment of acute gout.—If the gouty paroxysm occurs, as it most frequently does, in a great toe joint or foot, the limb should be slightly elevated above the level of the body, and a cradle arranged to take the weight of the bed-clothes off the affected part. To alleviate the severe pain a pack of cotton-wool should be arranged round the affected joint, and should be saturated with a warm soothing lotion, such as the following :—Sodæ carb. ʒiij., linim. belladon. ʒij., tinct. opii. ʒj., aq. ad ʒviij. A small portion of the lotion should be mixed with an equal quantity of hot water, and then poured on cotton-wool previously arranged round the joint. The pack should be changed every eight or twelve hours. No attempt at local depletion—such as the application of leeches to the inflamed joint, blistering or incisions—should on any account

be made. Nor should cold bathing or cold application to the joint be attempted. For the internal treatment of acute gout colchicum is a most valuable drug. It should be especially used for acute gout, and for subacute attacks supervening on chronic gout, as, if used continuously, tolerance is apt to be acquired, and then the drug ceases to act. It must be borne in mind that the susceptibility of some individuals to the action of this drug may necessitate caution in its administration. At the commencement a large dose of thirty to forty minims of colchicum wine should be given, followed by a mixture containing in each dose ten to twenty minims of the wine with from forty to sixty grains of citrate of potassium, which should be taken three times a day. The citrate of potassium is given for its combined properties of acting as a diuretic and of diminishing the acidity of the urine. Colchicum reduces the gouty inflammation, relieves the pain, and shortens the attack. It is a powerful direct cholagogue, and it is probably owing to its action on the liver, by inhibiting the formation of glycocine, and so diminishing the formation of uric acid in the kidneys, that the efficacy of colchicum in mitigating the severity of the pain and relieving an attack of gout is due. From three to four grains of blue pill should be given the first night, and should be followed by a dose of Epsom salts in the morning. In the employment of purgatives for gouty patients the great object is not to produce powerful purgation, but to relieve portal congestion. A very useful pill is one containing either two grains of euonymin or a quarter of a grain of podophyllin combined with a grain of extract of hyoscyamus and a grain and a half of the compound extract of colocynth. If the pain of an acute attack of gout is so severe as to prevent sleep, ten grains of chloral, sulphonal, trional, or phenacetin may be given, or a dose of one grain of extract of hyoscyamus given with blue pill at night will in some cases act as a very useful anodyne. It is doubtful whether salicylates are of any use in the treatment of true gout.

Diet in acute gout.—For the first day or two of an acute attack the patient should be restricted to a milk diet, which may consist of milk, arrowroot and milk, bread and milk, milk puddings made with rice, sago, or tapioca, and tea made with boiling milk instead of with water. Weak tea with cold toast thinly buttered may also be taken. The free drinking of hot or cold water, or of some mineral water free from sodium salts (see p. 223) should be encouraged. During the acute stage no alcohol should be given, unless there are strong reasons for its administration, such as a weak action of the heart, and a feeble irregular pulse, when a little well-matured whisky

diluted with an aerated water will prove the best form of alcohol. Beef-tea and any of the meat extracts or essences should be avoided at all times by gouty patients owing to the tendency they have to irritate the kidneys, and so to interfere with the elimination of uric acid. With the subsidence of the acute attack the patient may return to a more liberal diet (see p. 222).

Treatment of chronic gout.—The excessive formation of uric acid may be checked by careful attention to diet and regimen, by the promotion of the metabolism of the liver, and by the relief of congestion of the portal system.

In addition to colchicum, which may be given in small doses, guaiacum may very usefully be administered as an alterative which stimulates the metabolism of the liver, and also affords relief to the portal system. From five to ten grains of guaiacum resin should be given in cachets two or three times a day. If constipation occur, a sulphur and guaiacum tablet, or a dose of compound liquorice powder should be taken at night. An occasional dose of blue pill and euonymin followed by a purge of Epsom salts will be found useful. The elimination of uric acid may be promoted by encouraging free diuresis by the drinking of sufficient quantities of water, and by the administration of citrate of potassium, which increases the volume of the urine, and at the same time diminishes its acidity. The use of the citrate of potassium may with advantage be pushed until moderate alkalinity of the urine is produced. A patient suffering from gout should avoid, as far as possible, the use of common salt at table, on account of the power that it possesses of hastening the precipitation of sodium biurate.

To reduce the chronic inflammatory thickening of the fibrous tissues around gouty joints iodide of potassium may be given in doses of five to ten grains three times a day, and may usefully be combined with from five to ten minims of tincture of iodine. Careful massage, and gentle exercise of the stiffened joints should be employed, but only when convalescence is fairly established; massage and muscular movements increase the flow of lymph in the lymph channels and so tend to promote the removal of uratic deposits, and to increase general metabolism. If the œdema around a joint should persist, the hot douche followed by sponging with a cold strong solution of common salt will be found serviceable. The thermal baths of Bath, Buxton, Aix-les-Bains, and other spas, and mud baths are useful in the treatment of cases of chronic articular gout. The lithium salts, which have for some time had a reputation of being solvents of gouty deposits, probably do not possess any such

power, but since they are powerful diuretics they may, on that account, be of some use in the treatment of chronic gout. They should never, however, be given in sufficient quantities to keep the urine alkaline, as their depressing effect in such doses is too great. After convalescence as much exercise as possible, short of fatigue and discomfort, should be taken in the open air. Cycling is an excellent exercise for the gouty, since it furnishes good muscular movement in the open air without the gouty joints having to bear the weight of the body.

Treatment of retrocedent gout.—If the symptoms are urgent, some brandy should be given, and, if necessary, some morphine injected hypodermically, provided marked albuminuria does not exist. If the metastatic seizure affects either the heart or brain, it may be desirable to reinduce an attack of articular gout by placing the feet in a hot mustard-and-water bath. For the treatment of the cardiac form heart tonics and brandy should be administered, and a mustard-leaf applied to the epigastrium. If an anginal attack occurs, then, in addition, a dose of nitro-glycerine should be given at once, or an inhalation of nitrite of amyl employed. For the treatment of the cerebral form, if the patient is plethoric, if the pulse is hard, and stupor or coma supervene, venesection should be performed and from eight to sixteen ounces of blood withdrawn; in less urgent cases six leeches may be applied to the mastoid region. For the treatment of the gastro-intestinal form of retrocedent gout a mustard-leaf should be applied to the epigastrium, and a mixture containing bismuth subcarbonate, sodium bicarbonate, and hydrocyanic acid should be given.

Treatment of irregular gout.—One form of irregular gout, the gouty heart, is associated with fatty degeneration of the cardiac walls, and is generally evidenced by vertigo, faintness, palpitation, irregular pulse, insomnia, and slight anginal attacks. The treatment should be rest in the recumbent position, and a small dose of blue pill or calomel, followed by a purge of Epsom salts, should be administered. A mixture containing convallaria and strychnine may be given, and, if anginal attacks occur, nitro-glycerine or erythrol tetranitrate may be given by the mouth, or inhalations of nitrite of amyl employed. The patient must be carefully dieted, and graduated exercise, at first of a passive nature, such as the Schott treatment, and later of an active nature, may be very beneficial. For the treatment of gouty phlebitis, which is a fairly common form of irregular gout, the patient should be kept in the recumbent position, and any sudden movement of the affected limb must be

prevented, on account of the danger of detaching a portion of the thrombus and the occurrence of consequent embolism of the pulmonary artery. Equal parts of glycerine and extract of belladonna should be smeared over the affected part, and a linseed poultice, with some of the glycerine and belladonna spread on the surface, should be applied and renewed every six hours. In addition, the ordinary treatment of the gouty state must be resorted to. For the treatment of gouty sciatica the patient must be kept in the recumbent position, and in severe cases the pain should be relieved by a hypodermic injection of morphine. Ammonium chloride, in doses of thirty to forty grains three times a day, is a very useful drug in the treatment of this complaint. Two grains of salicylate of quinine should also be given in a pill two or three times a day, and in addition the ordinary treatment of the gouty state will probably have to be resorted to.

Treatment of gouty glycosuria and gouty diabetes.—Dietetic treatment should be resorted to without, however, restricting the diet too much. An excessively nitrogenous diet is to be avoided as tending to accentuate the gouty condition, but no hard and fast rules as to the amount of diet can be laid down. Each case must be treated by ascertaining what amounts of proteids, fats, and carbohydrates are best borne by the individual. Toasted bread, milk, and milk puddings made with rice, sago, and tapioca are generally permissible in this form of glycosuria. The best test of the suitability of the diet is the fact that the weight of the patient is not diminishing, while, at the same time, the excretion of sugar is becoming less. A pill containing one grain of blue pill, one grain of acetic extract of colchicum, and two grains of euonymin should be given every other night, and a mixture containing thirty grains of ammonium chloride and fifteen minims of dilute nitro-hydrochloric acid should be taken three times a day. The mineral waters best suited for the treatment of gouty glycosuria and diabetes are mentioned on page 197.

Preventive treatment of gout.—Whatever promotes the elimination of uric acid, and so prevents its absorption into the general circulation, tends to prevent the occurrence of gout. This can be effected by (1) the promotion of increased diuresis; (2) the production, at all events intermittently, of a moderate degree of alkalinity of the urine; and (3) stimulation of the metabolism of the liver, and of the kidney cells engaged in the excretion of uric acid. The first effect can be secured by the patient drinking a sufficient quantity of ordinary water, or of a suitable mineral water. The second object

is attained by the consumption of sufficient quantities of vegetable food, and by the occasional administration of citrate of potassium ; and the third by the administration of suitable cholagogues, such as guaiacum, and an occasional euonymin and blue pill. Careful attention should be given to diet. Regular habits and sufficient exercise should be encouraged, and constipation should be avoided.

Diet in gout.—A rational mixed diet is the one best suited for gouty patients. The assumption that a purely vegetable diet is best for the gouty is erroneous, since it makes no difference, as regards the production of uric acid, whether the proteid matter be of animal or vegetable origin ; but, since animal food is so much richer in proteids than a vegetable diet, the amount of the former taken by the gouty should be strictly limited. Due consideration should always be given to a patient's experience of what articles of diet disagree and agree with him. It is important that a gouty patient should take a sufficiency of water to drink, so that the various organs are well flushed, the removal of the gouty deposits encouraged, and the specific gravity of the urine kept moderately low. The quantities of fluids taken in the twenty-four hours should not be less than three and a half pints, and may even, with advantage, reach to four and a half pints. It is an excellent custom for a gouty person to slowly sip half a pint to a pint of hot water in the morning immediately after rising, and at night before retiring to bed ; if desired, the water may be flavoured with a slice of lemon peel. For breakfast a selection may be made from the following articles of diet :—porridge and milk, whiting, sole, plaice, fat bacon, and eggs cooked in various ways ; dry toast thinly buttered, and tea infused for three minutes should be taken with breakfast. At lunch and dinner no soup should be taken. The varieties of fish most suitable to the gouty are whiting, sole, turbot, and plaice. Meat should be taken at only one meal, and then in moderate quantity. Beef, mutton, chicken, turkey, pheasant, and calf's sweet-bread are admissible. Salted meat, salted and smoked fish, shell-fish, and articles of food pickled in vinegar should be avoided. Two vegetables should be taken at both lunch and dinner, and in abundant quantities. The vegetables that should be avoided by the gouty are asparagus, tomatoes, and green peas. Any of the other ordinary vegetables may be taken, of which the most useful are spinach, Brussels-sprouts, French beans, cabbage, turnip-tops, turnips, and celery. Stewed or baked fruits may with advantage be taken every day at one meal, and a milk pudding at the other meal. Rich pastry and all rich sweets should be avoided. As regards the employment of

alcohol, if the gouty person be of robust habit of body, then total abstinence is best. If, however, the cardiac action be weak and failing, then moderate quantities of alcohol should certainly be allowed. In cases of chronic gout, a moderate amount of alcohol may be necessary for the promotion of digestion. A tablespoonful of matured whisky freely diluted constitutes the best form of alcohol. Of wines, light but sound clarets and hocks are least open to objection. Port, burgundy, champagne, ale, and stout should be avoided by the gouty.

Mineral waters in the treatment of gout.—The value of a given mineral water in the treatment of gout depends greatly on the main object with which it is taken, whether to remove gouty deposits, or to stimulate the action of a sluggish liver and to relieve portal congestion, or for the treatment of gouty dyspepsia, or to relieve the bowels in cases of torpor and gastro-intestinal catarrh, or to act on the kidneys, or to relieve gouty affections of the skin. The use of a mineral water, so far as its employment with the object of removing gouty deposits is concerned, lies solely in its watery constituent, and does not in any way depend on the mineral constituents dissolved in it. For such a purpose the springs which contain no sodium salts, or traces only, are the ones suitable for such cases; these are the simple waters classified in group 1. In cases of sluggish action of the liver, of gastro-intestinal catarrh and torpor, of gouty dyspepsia, and of other forms of irregular gout, mineral waters containing sodium salts are beneficial, owing to the action of these salts as hepatic and gastro-intestinal stimulants. The various mineral waters used in the treatment of gout may be classified into the six following groups:—

1. *The simple waters, or waters comparatively free from sodium salts.*—These are the waters that are especially useful for the removal of uratic deposits in the joints and tissues. The principal waters of this class are those of Buxton, Bath, Strathpeffer, Con-trexéville, Aix-les-Bains, Pfæfers, Gastein, Wildbad, and Vittel.

2. *The simple alkaline waters.*—These contain sodium bicarbonate, and are useful for the treatment of hepatic congestion, dyspepsia, and gastro-intestinal catarrh. The principal waters of this class are those of Vichy, Vals, Neuenahr, Salzbrunn, and Fachingen.

3. *The alkaline sulphated waters.*—These contain sodium bicarbonate and sulphate, and generally a moderate proportion of sodium chloride, and are useful for the treatment of the same class of disorders as mentioned in the previous group. The principal

waters of this class are those of Carlsbad, Marienbad, Tarasp-Schuls, Cheltenham, and Leamington.

4. *The alkaline muriated waters.*—These contain sodium bicarbonate and chloride, and are useful for the treatment of gouty dyspepsia, and of gouty catarrhal affections of the respiratory organs. The principal waters of this class are those of Ems, Royat, Assmannshausen, and La Bourboule.

5. *The muriated waters.*—These contain sodium chloride as their principal constituent, and are useful for the treatment of gastrointestinal and hepatic gout, and gouty dyspepsia. The principal waters of this class are those of Homburg, Wiesbaden, Kissingen, Baden-Baden, Nauheim, Llandrindod, Woodhall Spa, and Llangam-march Wells.

6. *The sulphur waters.*—These contain sulphur, either in the form of sulphuretted hydrogen only, or, in addition, some of the sulphur may exist in the form of the sulphides of calcium, magnesium, and sodium. They are useful in the treatment of gouty skin affections. The principal waters of this class are those of Harrogate, Strathpeffer, Aix-les-Bains, Aix-la-Chapelle, Baden, Llandrindod, and Weilbach.

ARTHUR P. LUFF.

RHEUMATOID ARTHRITIS

SYN. ARTHRITIS DEFORMANS

Few diseases have been known under so many names as rheumatoid arthritis. Osteo-arthritis, chronic rheumatism, rheumatic gout, and arthritis deformans are some only of the designations which denote the variety and confusion of views held concerning its nature. Formerly there was a lack of definition as to what was and what was not rheumatoid arthritis, and it was made to embrace many cases of gout on the one hand and rheumatism on the other. Even now, with a more accurate demarcation, it is open to doubt whether the varieties of rheumatoid arthritis presently to be described are one and the same disease.

Etiology—*Age and sex.*—Chronic polyarticular rheumatoid arthritis is very much more prevalent among women than men, the

proportion being about five to one. The most numerous cases are found in middle life, the maximum for women being reached between forty-five and fifty, and for men a few years later. On the other hand the acute cases are found amongst children and young people, and in children the males suffer as much if not more than the females. The more chronic mono-articular type, in contrast to the foregoing, affects men more than women and is a disease of life's decline.

The variety affecting the joints of the fingers, and conveniently termed Heberden's nodes, belongs chiefly to the second half of life and to the female sex.

Heredity.—The confusion in nomenclature makes it difficult to determine whether the disease is directly inherited. Inquiry has, however, shown that joint troubles, styled indifferently gouty or rheumatic, are more common amongst the ancestors of rheumatoid patients, and that there is probably an inherited predisposition to arthritic disease which may manifest itself as gout, rheumatism, or rheumatoid arthritis according to circumstances. Tubercle often figures in the family history, and is regarded as a predisposing cause. It probably has only an indirect influence, and denotes low resisting power.

Enfeebled vitality.—All conditions which seriously depress the health of body or mind are amongst the most important causes of the disease. Food, insufficient in quantity or bad in quality, and unhealthy dwellings are examples of the one; mental distress, either as an acute short-lived fear or long-continued anxiety, are examples of the other. Thus, too, may be explained why the disease is an occasional sequel of influenza, and why it is seen in relation to the menopause, catamenial disturbances, and the exhaustion of prolonged lactation and too frequent parturition.

Injury.—Rheumatoid changes are liable to follow injury to a joint or the soft parts near it, and, of greater interest still, this local arthritis may exceptionally become generalised.

Other arthritic diseases.—Joints that have been the seat either of acute or subacute rheumatism, gonorrhoeal synovitis, or gout, exhibit on that account a greater proneness to rheumatoid attacks. This is especially the case with rheumatism, close on the heels of which rheumatoid arthritis will follow, and it may be difficult to say where the one ended and the other began, or whether the whole illness has not been acute rheumatoid arthritis from the outset.

Morbid anatomy.—The joints are enlarged and, it may be,

deformed. The synovial membrane is thickened, and in the acute stages vascular and soft, but in cases of long standing pale and hard. The synovial fringes are enlarged, and deposits of cartilage may be formed in one or more of them. The synovia is increased in amount except in the most chronic cases. Ligaments are, in acute conditions, swollen and inflamed, and may be absorbed; in chronic conditions they cannot be differentiated from the fibroid thickening of the joint capsule. The periarticular tissues undergo considerable thickening, and in later stages, when they become hard, contracted, and adherent, contribute largely to the limitation of joint movement. In old-standing cases deposits of bone and cartilage are formed on the inner aspect of the capsule. The cartilage is soft, and has the appearance of velvet pile owing to its matrix at the surface being split up into fibrillæ. This fibrillation is in part brought about by the changes in the cartilage cells. These multiply, distend their capsules, and those of the latter which are near the surface empty their contents into the joint, leaving spaces, between which the matrix is split up into filaments. The changes subsequent to the early proliferation of the cartilage differ in the centre and the periphery of the articular surface. In the centre the cartilage is gradually worn down first at the points of greatest pressure, and if the process advances the bone will become quite denuded. The bone thus laid bare differs in appearance according to the length and intensity of the disease. In acute conditions it is soft, red, and eroded, whereas in the chronic it is condensed, highly polished, eburnated, and often grooved, or hollowed by the constant friction with the similarly conditioned surface opposed to it. The superficial layer of dense sclerosed bone is but a thin one, and the epiphysis subjacent to it shows rarefaction and slowly progressive atrophy which may lead to shortening. Side by side with this destruction in the centre there is overgrowth of cartilage at the periphery, which undergoes secondary ossification. These bony and cartilaginous deposits are of varying and irregular shapes, and project from the margin of the articular surface, enlarge the end of the bone, and produce what in life is felt as "lipping." The degree to which this deposition of cartilage and bone at the periphery takes place differs according to circumstances. In cases that are acute it is comparatively slight, and skiagrams show that the ends of the bones are not enlarged, whereas in those that are chronic it is considerable. Except, however, where the disease attacks the vertebræ there is no true ankylosis, but the articular surfaces are rather surrounded by fibrous thickening and bony deposit which may constitute so rigid

a casement as to cause almost complete immobility of the joint. Less often the bony outgrowths will produce dislocation.

The muscles show well-marked atrophy. Definite peripheral neuritis has been demonstrated in a few cases, though not of the nerves which actually supply the joints. No changes in the spinal cord have as yet been certainly described, except where the disease has attacked the vertebral articulations and the cord and nerve roots have been secondarily affected.

Where the joint changes have been very acute the lymphatic glands of the extremities are sometimes found to be enlarged, and in children the spleen also.

Heberden's nodes are small, bony outgrowths from the third and less often from the second phalanges of the fingers close by the articular surfaces; they are covered by a projection of the synovial membrane. Erosion of cartilage and eburnation of bone are slight or even absent.

Clinical manifestations.—The disease presents itself in life under forms which are widely different, and may be grouped as follows:—

1. **POLYARTICULAR RHEUMATOID ARTHRITIS**, in which there is a simultaneous and symmetrical invasion of many joints, usually the smaller peripheral ones, accompanied by bodily ill-health and anæmia, and certain trophic manifestations, such as muscular atrophy, local sweating, and pigmented and glossy skin.

2. **LOCALISED RHEUMATOID ARTHRITIS**, in which the joints attacked are larger, single or few in number, and near or in the trunk; where there is no symmetry of invasion, few and very slight trophic manifestations, and no appreciable disturbance of health.

3. **HEBERDEN'S NODES.**—This form shows the symmetry and peripheral invasion of the polyarticular type, but is localised to the fingers and is very chronic.

POLYARTICULAR RHEUMATOID ARTHRITIS

This form of the disease has two varieties—the acute and the chronic.

The **ACUTE FORM** occurs especially in young adults and children, and in the male sex equally with the female. The joint invasion may be preceded by such premonitory symptoms as tingling, sweating, tachycardia, and neuralgic pains, and of the latter special significance is attached to those felt in the ball of the thumb and the ulnar side of the wrist; or without warning joints will swell in



FIG. 18.—The hands of rheumatoid arthritis, showing ulnar deflection and joint deformities.

Photographed by E. H. HARNACK.



FIG. 19.—Skilograph of the same hands showing destruction of cartilage; exostoses; and rarefaction and destruction of bone in the terminal joints of the left-hand figure.

Radiographed by E. H. HARNACK.

rapid sequence, commencing usually in the fingers. The enlargements are soft, elastic, and hot to the touch; those of the fingers often fusiform in shape; they are chiefly due to excess of fluid and to swelling of the synovial membrane and fibrous structures of the joint. The enlargement of the bones is not appreciable, and no bony outgrowths are perceptible. The destruction of cartilage is rapid, and crackling can be detected on manipulation. There is much pain both at rest and on movement, and considerable tenderness. The skin over the affected joints assumes a dusky red appearance.

Muscular atrophy and spasms, increased reflexes, local sweating, impaired movements, and deformities, all of which will be more fully referred to under the more common chronic variety, supervene rapidly. There are fever, increased pulse rate, sometimes enlargement of the glands near the affected joints, wasting, cachexia, and considerable anæmia.

In a few weeks the mischief subsides or passes on into the chronic form, but the joint destruction is appalling and the patient is often left a helpless cripple.

CHRONIC FORM.—In this, the much more common variety, the distribution of the disease is the same as in the acute form, but its progress is more slow and the constitutional symptoms less marked. The mischief begins mostly in the smaller joints, and in two-thirds of the cases in those of the hands. It extends to the larger joints, and in severe cases may involve nearly all the articulations of the body, including those of the spine and lower jaw.

The swollen joints feel firm and resistant, the periarticular structures are thickened, the ends of the bones are enlarged, bony outgrowths can be felt, movement is impaired and accompanied by pain and grating. There is wasting of muscles, not only in the region of the joints, but away from them; it is selective, showing a bias for the extensors and the small muscles of the extremities, especially the interossei; it may be accompanied by muscular spasms, tremors, and increased reflexes, but reaction of degeneration is absent unless there be neuritis.

The disorganisation of the joints, the wasting of some muscles and the spasms of others, lead to deformities and dislocations. In the hands very characteristic appearances are thus produced. The metacarpo-phalangeal joints, especially those of the index and middle fingers, and interphalangeal joints are enlarged, the small muscles are wasted, the fingers as a whole are deflected to the ulnar side, and less often their terminal phalanges to the radial side. This peculiar and constant ulnar deflection of the fingers has been attributed to

the unopposed action of the extensor communis digitorum—from weakness of the interossei. There may further be deformities of flexion and extension, dependent very much on the condition of the interossei. These latter flex the first phalanges and extend the second, so when they are weak there would tend to be extension of the first phalanges and flexion of the second and *vice versa*. Flexion of the first phalanges on the metacarpals is a far more common appearance than extension. A usual combination with the former is extension of the second phalanges on the first and flexion of the terminal phalanges on the second, and the reverse combination with the latter. But the positions of the phalanges more often show variation, e.g. flexion of the metacarpo-phalangeal joints may be accompanied by extension of the second phalanges on the first and of the terminal on the second. Deformities occur in the lower limbs from similar causes. Joints become dislocated sometimes from muscular atrophy and subsequent shortening, and sometimes by the osteophytic outgrowths.

There are other trophic phenomena. The hands and feet are cold and clammy; the skin is glossy and often pigmented, exhibiting irregular patches somewhat resembling freckles, but of a burnt sienna colour and not limited to exposed situations; the nails are ribbed and devoid of lustre. Occasionally there is peripheral neuritis. Subcutaneous fibrous nodules are sometimes a feature of this disease as well as of rheumatism.

The pain of the disease varies. In some cases it is so severe as to necessitate recourse to morphia, while in others it is bearable. In character it is gnawing, and is increased by the warmth of bed and by movement. It is variously caused; sometimes it has its origin in the joints, at other times it is due to muscular spasm, or it may be neuralgic. The pulse may be increased in frequency and tension and there may be palpitation, but there are no cardiac lesions and, speaking generally, constitutional symptoms are slight, though some degree of pallor and weakness is the rule. Deafness is common, and probably results from ankylosis of the ossicles. After varying periods the disease will often be arrested and pain will almost cease, and the patient enjoys as much health as her maimed condition permits. The continuous progress of the case, however, is frequently marked by exacerbations of pain, and it may be also by rises of temperature. These last an indefinite time, and are followed by as long or longer periods of almost complete freedom from discomfort, and a remarkable degree of aptitude with seriously crippled hands may come to be acquired.

A form of rheumatoid arthritis, of which the severity justifies the appellation subacute, is not infrequently seen in women at about the age of thirty or even less. It is associated with premature menopause and with varying symptoms of neurosis. It speedily affects all four extremities, and having completely crippled the subject abates, leaving permanent and irremediable deformity.

LOCALISED RHEUMATOID ARTHRITIS

This variety, unlike the foregoing, has the features of a local rather than a systemic disease, attacks single joints, has for its favourite seats the hip and shoulder of elderly people, and is frequently related to slight injuries. The two important manifestations are pain and limitation of movement. Pain is of a gnawing character, and is worse on first going to bed and with the first efforts at movement after a period of rest; it is referred to the affected joint, and often, in the case of the hip, to the knee also. There may be considerable muscular atrophy—thus in the case of the hip, the buttock may be flattened, the fold of the nates gone, and the measurement round the thigh less than on the unaffected side. Grating on movement can usually be detected, and where the joint is accessible to examination the characteristic lipping and capsular thickening. Cysts originating from and sometimes communicating with the articulation are met with. When the hip is affected, the knee-jerk on the same side and occasionally also on the opposite may be exaggerated. As the case progresses, the stiffness increases and the power and range of movement diminish. In the case of the hip or shoulder there may also be considerable shortening, owing to destruction and atrophy of the heads of the bones. In all but the worst cases, however, the joint retains some degree of usefulness. This variety, though commonly mono-articular, does not always confine its depredation to a single joint. A rheumatoid hip is sometimes accompanied by similar though slighter changes in a shoulder, or it may be in the lumbar vertebræ. Rarely also what begins as a localised arthritis will develop into the generalised form of the disease.

Rheumatoid arthritis of the spine manifests itself, as other forms do, by pain and impaired mobility. It is more often found in the cervical region than elsewhere, when the movements of the head and neck are seriously restricted. Rarely the whole length of the spine will be involved, and the vertebræ become welded by bony and fibrous union into a rigid column.

HEBERDEN'S NODES

The enlargement of the finger joints is accompanied by limitation in the power and range of movement, and sometimes in the earlier stages by pain and tenderness. The process is very chronic, and carries with it but slight predisposition to the more severe forms of the disease, although it will sometimes accompany them.

RHEUMATOID ARTHRITIS IN CHILDREN

Among the various forms of arthritis met with in children, exclusive of the rheumatic, gonorrhœal, tuberculous, syphilitic, and acute septic, are cases which conform in all particulars to the description of the acute and chronic polyarticular rheumatoid varieties above set forth. Others, and perhaps the majority, differ in several essential features and have received special investigation by Dr. Still (*Tr. R. Med. Chi. Soc.* 1897, vol. lxxx.). The malady, which commences before the second dentition, even as early as fifteen months, does not exhibit a marked preference for females, nor are the joints affected in the same way as in rheumatoid arthritis. There is an "absence of bony change even when the disease is advanced," and the cartilage does not show the characteristic fibrillation; rather is it a periarticular thickening that causes the round and fusiform swellings, which are usually painless and seldom red. In contrast to the early invasion of the small joints of the hand, this condition generally begins in the knees and wrists, which may be alone affected for a long period. "Limitation of movement, chiefly of extension, is almost always present; the child may be completely bedridden owing to more or less rigid flexion of joints." The deformities of the hands are only moderate in degree. There is considerable muscular wasting. The lymphatic glands are more frequently and extensively enlarged than in adults, and "primarily and chiefly those related to the affected joints"; they are discrete, hard, not tender, and with no inclination to break down. There is often also enlargement of the spleen. (It has been objected that the facility with which the glands and spleen enlarge in children diminishes the value of these conditions as characteristic of the affection.) Among general symptoms are anæmia, sweating, often profuse, a very variable pyrexia, and an arrest of the bodily development. As in the allied forms it is a progressive malady and not of itself fatal.

Pathology.—Many difficulties and conflicting views surround

the pathology of rheumatoid arthritis. It will clear the ground to discuss first its relations to rheumatism and gout, with which distinguished authorities have connected it. Granted that rheumatoid arthritis may accompany or follow rheumatism and gout, this association does not prove their identity. In rheumatoid arthritis the structural changes in the joints are distinctive and exist in every variety of the disease. Recall also the impaired mobility, the muscular wasting and other trophic signs, the steady progress from joint to joint with, at best, incomplete recovery, the absence of visceral lesions and the age and sex most prone, and it is clear that rheumatoid arthritis is not "rheumatic." Nor is it "gouty": it affects the ill-conditioned rather than the well-conditioned, women rather than men; it has not the same geographical distribution; there are no biurate of soda deposits, and the well-known visceral manifestations of gout are not found in association with it.

The neural theory.—Many considerations that are weighty point to the disease being of nervous origin—some derangement of the nerve centres disturbing the nutrition of the joints. The frequently symmetrical invasion, the muscular atrophy, and the disproportion between the joint changes and its amount and distribution, the increased reflexes, the changes in the skin and nails are all suggestive of a nervous causation. The structural changes in the joints too show, especially in the acute polyarticular variety, a striking resemblance to those found in locomotor ataxy and syringomyelia, which are admittedly dystrophic. No changes, on the other hand, have as yet been certainly demonstrated either in the spinal cells or in the nerves which supply the joints. And when occasionally neuritis is present, it is an incident rather than a cause of the disease.

The microbic theory.—In the fluid and tissues of the joints of acute rheumatoid arthritis a micro-organism has been constantly found (Bannatyne, Wohlmann, and Blaxall). It is a very small bacillus ($2\mu \times 0.6\mu$) exhibiting bipolar staining. For clinical purposes it is most easily shown by mixing a drop of the synovia with a few drops of aniline methylene blue on a cover glass, drying slowly over a Bunsen flame and fixing by passing through it, and then washing freely, drying, and mounting. The bacillus is found in the synovial fluid, synovial membrane, cartilage and bone of rheumatoid articulations, and even occasionally in the blood. It has not been found in joints affected by other diseases. Pure cultivations of the bacillus have been obtained in peptonised beef broth, and on agar-agar and blood serum. In the beef broth the colonies of bacilli

appear four days after inoculation as small particles resembling gold-dust. Experimental inoculation has not so far been successful in reproducing the disease, and consequently the causal relation of the bacilli to it lacks proof. On the other hand, it cannot be said that the failure of experimental inoculation is ground for dismissing the microbic theory of the disease, for the same gap in the evidence exists in the case of influenza as to the bacillary origin, of which there is no doubt. The existence of the above bacillus and its relation to rheumatoid arthritis have not yet gained general acceptance by bacteriologists. Further observations are doubtless needed. Many of the features of the disease, especially the acute variety, are, however, explicable by the microbic theory of origin. The symmetrical invasion, the nervous accompaniments, such as muscular atrophy, sweating, and skin changes; the fever and rapid course of the acute cases and the tachycardia can be accounted for by the presence of some toxin circulating in the blood. The view put forward by Bannatyne and his fellow-investigators is that the bacilli have the joints for their habitat; here, by their local action, they set up the cartilage destruction and other joint changes and produce toxins which circulate in the blood and derange the function if not the structure of nerve centres. There is nothing widely inconsistent between the neural and microbic theories. It is quite possible to modify the latter, and suppose that the joint changes are trophic and are produced by the action of the toxins on the nerve centres and not by the local action of the bacilli. Nor does analogy make this view less probable, for many of the features of infantile paralysis and other forms of myelitis suggest an infective origin. As long as discussion is restricted to the polyarticular variety of the disease, the neural and microbic theories have the support of many facts, but it is different when the other varieties are considered.

In the case of a chronic rheumatoid hip or Heberden's nodes there is little to suggest a neural, and everything to negative a microbic origin. It might be held that the inability of these theories to explain all forms of the disease weakens the probability of their truth. On the other hand, the question is suggested whether localised rheumatoid arthritis and Heberden's nodes are, strictly speaking, the same disease as the polyarticular arthritis. There are grounds for thinking that perhaps they are not. They differ in their mode of onset, their freedom from constitutional and trophic disturbances and the sexes and ages they favour. In one important respect they agree, however, and that is in the substantial similarity of the structural changes in the joints. It may be that identical

morbid changes have different causations, and in the one case are due to a systemic and in the other to a local disease. But the difficulties are great, more knowledge is needed, and a confident opinion would be premature.

Diagnosis.—Where the characteristic deformities and pains are present this as a rule presents no difficulty. But when the symptoms are ill-defined it is different.

From *acute rheumatism* there is not often difficulty except with the rarely occurring acute polyarticular variety. In rheumatism there is no destruction of cartilage and no periarticular thickening, while in rheumatoid arthritis the reverse is the case. The swellings are migratory in rheumatism, receding from one joint and invading another, and cardiac lesions are common, whereas in rheumatoid arthritis the mischief visits a joint to stay, and cardiac lesions are unknown, except incidentally. In cases of rheumatism there is often a history of chorea, tonsillitis, and other rheumatic manifestations. The liability of rheumatoid arthritis to follow acute rheumatism must not be forgotten.

From *gout* the difficulty only arises with the chronic forms, and at times may be very great. In gout the joint changes are different, and the history of acute attacks, especially in the big toe, the presence of tophi and other urate of soda deposits will make the diagnosis clear (see p. 215).

In *gonorrhœal arthritis*, fibrous adhesions are liable to form early; there is no grating; there is a history of urethral discharge, and the subject is more often young and of the male sex. If the case is of longer standing, the difficulty does not often arise, for the bony lipping and deposits of the rheumatoid joint will be more apparent.

Where there is swelling of a single joint, rheumatoid arthritis has to be distinguished from diseases beyond those already mentioned. Such are the arthropathies of *tabes dorsalis* and *syringomyelia*. These may be distinguished by the acuteness of their onset, their location in a single large joint, the absence of pain, and the characteristic nervous symptoms which accompany them. When a single joint, such as a knee, is enlarged, very tender and painful, the possibility of sarcoma being the cause must be kept in mind. Where muscular atrophy of the upper limb, say about the shoulder, is a prominent feature and pain is slight, progressive muscular atrophy might be thought of, but an examination of the joint would soon make the diagnosis clear. Where pain is a predominant symptom, and other evidences of rheumatoid arthritis are ill-defined, the

pitfalls are numerous. Thus neuralgia and myalgia may have rheumatoid arthritis underlying them. Sciatica may be mistaken for a rheumatoid hip. The soft parts covering the joint prevent close examination, though grating can usually be felt, and sciatica is accompanied by muscular wasting and its pain leads to voluntary limitation of movement. A pain in the back, in reality due to rheumatoid changes in the vertebral joints, may be ascribed to spinal disease, and if low down to one of the many causes of lumbar pain, such as lumbago, uterine disorders, neurasthenia, or hysteria. Rigidity of spine and rheumatoid changes elsewhere (*e.g.* the fingers) will, if present, point to the true cause of the pain.

As an aid in diagnosis the X-rays may be employed, for by them the osteophytes are clearly recognised.

Prognosis.—The disease is a discouraging one, and, though rarely fatal, frequently makes life a burden. When once the cartilages are destroyed the recovery of the joint involved is beyond hope, and it is only possible to relieve the pain and stiffness that have ensued and prevent the extension of the disease if possible to other joints. In the early stages, before the cartilage of a joint is destroyed, an even considerable degree of swelling and effusion may subside, and mobility be restored under appropriate treatment. It thus follows that early diagnosis and treatment are very important.

In the acute polyarticular variety, fortunately rare, no treatment, however early, is of any avail, and the mischief progresses rapidly, leaving the victim completely disabled.

The localised form, of which the hip joint is so common a seat, progresses but slowly, though it often obstinately resists treatment.

Treatment.—This falls under the headings of general and local. Under general treatment the most important indication is to maintain health and contentment in every way possible—by diet, climate, and cheerful surroundings, and avoidance of bodily and mental strain. In the rare acute polyarticular variety, rest in bed and a simple nourishing diet are required.

In the more common chronic forms it is different, and what follows applies to them. Here the diet should be generous and free of any restrictions save those that are necessary for the avoidance of digestive derangement. Wine, beer, or stout with the meals is often of advantage.

Exercise is limited by the very nature of the infirmity. It should be persevered in notwithstanding stiffness and even some pain during movement, though it should not be such as to cause an enduring pain after it. Fresh air is essential both within and with-

out the dwelling ; rooms should be airy, though warm and equable, and the amount of outdoor life should be considerable if the weather is not damp or too cold. The wearing of light woollen underclothing is imperative. For climate, one that is dry, warm, and equable is the best, and for this reason wintering away from England is beneficial, provided the disease is not too advanced for the fatigues of travelling and the deprivation of home comforts and associations.

Drugs.—Arsenic, iron, and iodides, and combinations of these give the best results. Iodide of iron, either as the syrup (℥ 20 to 30), or in pill (gr. 3), deserves special mention. Quinine in doses of one or two grains does good in virtue of its tonic action. Guaiacum sometimes does good. Cod-liver oil often exercises marked benefit, but can often only be borne in cold weather. All remedies need to be taken over long periods of time to effect any good results. For the relief of pain sodium salicylate, and less often phenacetin, are effective. Opium and morphia should, generally speaking, be avoided, and where, through the intensity of the pain, they become necessary, great circumspection is needed to avoid the habit being contracted.

Treatment at spas.—Marked benefit undoubtedly follows this in suitable cases, and may be ascribed in part to the invigorating effect of climate and surroundings on health and spirits, and in part to the local actions of the waters on the joints.

The chemical composition of the springs does not appear to be of prime moment, but rather their general environment and their mode of application to the joint. In England, Bath, Buxton, Droitwich, and Harrogate are widely resorted to ; and abroad, Aix-les-Bains, the ferruginous waters of Spa, Schwalbach, or S. Moritz, and La Bourboule and Mont Dore, which are arsenical.

The best local treatment for the joints is douche massage combined with gentle passive movements, as carried out at Bath and Aix-les-Bains. The patient resting in a bath, the joints are rubbed under a spray of water maintained at a temperature of about 110° F. during the sitting and cooled down at the end of it. Although carried out with greatest advantage at selected spas, this treatment can with proper appliances be effected anywhere, and though only non-medicated water may be available, great good will accrue. Electrical baths have yielded good results, but need special appliances and knowledge. The bath is made of non-conducting material, the poles are placed at the two ends near but not in contact with the patient, who is just covered with water at about

100° F. Either a constant or alternating current may be employed, and its strength should be increased and decreased gently.

Local measures for the relief of pain comprise protecting the joints with cotton wool, supporting them lightly with felt or flannel, and the application of glycerine of le'ladonna, tincture of iodine, the liniment of chloroform, or methyl salicylate or guaiacol mixed with olive oil (1 to 3). Hot boric dressings have been recommended in acute cases. Local vapour baths, or the topical application of dry air heated to 250° F. or 300° F. will relieve pain, but it is doubtful if they have any curative action. General vapour baths are to be deprecated as being too weakening.

BERTRAND DAWSON.

CHRONIC RHEUMATISM

This term had formerly a far wider range of application than it has at present. Many diseases that have now been differentiated as rheumatoid arthritis, chronic gout, and gonorrhœal arthritis were included, together with those cases to which the name may with some propriety be applied. If the word "rheumatism"—which originally signified a "rheum" or fluxion, synonymous with "catarrh"—be taken to signify, as it commonly does, pains of a mild or severe, transient or lasting character, felt in and about the joints, and associated with the idea of a chill or cold for their cause, then it is clear some qualifying terms, such as traumatic, gonorrhœal, gouty, etc., are required when these pains are considered in reference to their etiology. But the name has by common consent become specially connected with that symptom-complex which we recognise as acute rheumatism or rheumatic fever, in which the arthritic changes are only some of the phenomena present. It would seem to follow, then, that "chronic rheumatism," if permissible at all, should express those morbid conditions which, presenting the general features of chronic disease, bear a definite relationship to the acute malady. It will be seen, however, that, as generally used, many cases are therein included which have a very doubtful connection with a previous rheumatic fever. From all which it would appear that the term is of very uncertain and

indefinite application, and whilst still frequently employed in a vague way to express arthritic, muscular, and neuralgic pains in the limbs, it is probably falling into disuse as a term of precision. As at present employed, two groups of cases are comprised within the expression "chronic rheumatism": those which apparently trace their origin to a previous rheumatic fever, and those where no such antecedent is to be recognised. But no distinction can be drawn as regards clinical characters or morbid appearances in the joints, although the marked differences often exhibited in response to treatment does suggest some underlying real distinction. It is obvious, therefore, that too much importance cannot at present be attached to any such separation of cases. If it were certain that some of them were the direct sequel of the rheumatic intoxication, and that others as certainly were not, the distinction would no doubt be important, but this cannot be affirmed. It is possible that with increased knowledge a further differentiation of the numerous and imperfectly understood cases now called chronic rheumatism may be effected, but this can only be when their etiology is more accurately known. The similarity of symptoms, and, except in a few points, the resemblances of structural change in the affected regions, no doubt formerly caused all these chronic articular lesions to be indiscriminately lumped together, from which such forms as gouty and gonorrhœal arthritis have been successfully distinguished. The whole subject requires, for its complete understanding, much further investigation, with a rational appreciation of those numerous cases which appear to combine the symptoms of several groups—intermediate cases; and at the same time a recognition of those distinctly trophic joint lesions seen in tabes and syringomyelia, and the chronic myalgias and neuralgias with which chronic rheumatism so-called is so constantly associated.

Symptoms.—The present-day conception of acute rheumatism is one that regards it as a malady of an infective character, manifesting itself by a febrile state with cardiac, arthritic, cutaneous, tonsillar, and other symptoms, in varying degree of combination and occurrence. The joint changes, however mild or however severe, are in the great majority of cases of a temporary and entirely recoverable character, leaving no subsequent effect, such permanent results as are met with being chiefly connected with the heart. In a very small proportion of cases of acute rheumatism, and chiefly in those of adult or middle life, more or less permanent arthritic changes are developed; a few, but only a few, of the cases of rheumatoid arthritis come within this category, and the remainder

are included within the term chronic rheumatism.¹ It has been suggested that to these last the name "chronic rheumatic arthritis" should be given, and this would have the merit of indicating the relationship to acute or subacute rheumatism, and the specially arthritic nature of the affection.

Instead of the complete subsidence of the pain, swelling, and frequent redness which characterise acute articular rheumatism, one or perhaps several of the joints may continue stiff and painful after the temperature has been normal and other symptoms have disappeared. There is probably some swelling, though not invariably so, and when the joints of the fingers present this condition it may be fusiform in shape. What it is that determines this continuance, rather than recovery, it is at present impossible to say, though there is reason to believe that joints which have been the seat of previous injury, even such as a slight sprain, may have thereby lowered their power of resistance, and so prevented complete restoration to the normal state. Or it may be that the joint or joints appear to have quite recovered, and that it is only after some interval they may become painful and stiff, and possibly swollen, and remain so, without any febrile or other symptoms.

In contrast to the foregoing, so far as apparent causation is concerned, are the numerous cases of chronic articular disease in which no history of previous rheumatic fever is obtainable, such as the "rheumatics" of later life, and of those who have been subjected to long-continued exposure to cold and damp. Apart, however, from the fact that such negative history is far from being always reliable, it is none the less true that other individuals of the patient's family may have so suffered, suggestive, may be, of some constitutional liability. There is pain, and perhaps swelling, of several joints, or only of one, such as hip, shoulder, or knee, with what appears to be very characteristic of these cases, a very close dependence of the degree of pain and discomfort on the state of the weather; cold and damp, or an east wind, with its singularly virulent qualities, determining an exacerbation of symptoms which defies treatment until the weather changes. Sometimes the pains are much worse at night; in other cases this is not so, but exposed localities, and especially a clay soil, are potent in maintaining, if not in causing, this condition.

¹ The application of the term "chronic rheumatism" to those cases, so frequently met with, where, over periods of months or even years, repeated attacks of one or more of the rheumatic manifestations occur, appears to the writer to be inappropriate; the word "recurrent" seems more correctly to express this condition.

Morbid appearances.—However chronic the disease may be, it is noticeable that the internal structures of the affected joints—the cartilages and bones—exhibit but little if any change; such thickening as may be present is chiefly due to alterations in the ligamentous and other structures external to the joint, which cause the impairment of movement, and often a creaking sound, distinct from the grating of opposed bony surfaces, is to be heard on manipulation. Occasionally shifting from joint to joint, the tendency is to settle on one or several of the articulations, and slowly to impair their efficiency. The extent to which the joint is crippled is very variable, but the deformity rarely becomes so great or so general as it frequently is in rheumatoid arthritis, when the bony and cartilaginous tissues of the joint are so profoundly affected. Yet from time to time cases are seen which appear to be intermediate in their characters. Some atrophy of the muscles connected with the affected joints may take place, in fact, no doubt, from disuse; and contracture of some muscles may be observed contributing to the deformities which occur. There is not infrequently some fibroid thickening of the vessels and even of the cardiac valves.

The grounds upon which a differential **diagnosis** can be made between chronic rheumatism, as here defined, and chronic gouty arthritis or rheumatoid arthritis—the diseases for which it is most likely to be mistaken—are sufficiently indicated in the descriptions of those maladies. From gonorrhœal arthritis, or from chronic articular changes developed in syphilis, a history of specific infection should serve as the distinguishing feature, since in clinical characters these conditions are much alike.

Treatment.—Whilst many sufferers from this complaint receive but slight benefit from treatment, for others much may be done. Speaking generally, those are the most hopeful which are most recent, and are distinctly rheumatic in origin. The effect of the sodium salicylates, often very advantageously combined with small doses of the iodides, is most marked in those where a previous acute rheumatism has occurred, whilst in those essentially chronic cases without such history the drug has little or no effect in this respect, resembling its general uselessness in rheumatoid arthritis. This difference in behaviour of these affections under salicylates is of some diagnostic value. When they fail, the iodides alone may relieve, and this is especially likely to be the case when the pains are mainly nocturnal. Guaiacum, as in the form of *Mistura Guaiaci* BP, was formerly held in high repute, though lately much less prescribed; it is certainly of use in some cases, though it is not easy to foretell which.

Local applications to the affected joints in the form of stimulant liniments, painting with tinct. iodi., or blisters, are occasionally of service; much more beneficial are hot douches of plain or saline waters, accompanied with properly administered friction. The treatment at such watering-places as Droitwich, Bath, Buxton, and Aix-les-Bains is often most efficacious; or the recently introduced dry heat of considerable elevation will sometimes effect most satisfactory results.

Removal from a damp or clay soil, and residence in a warm, preferably dry climate, and warm woollen clothing, are essential. There appears to be no special need for any particular dietetic restrictions.

W. H. ALLCHIN.

MYALGIA

Myalgia is a general expression covering all varieties of pain referred to voluntary muscles. It comprises many widely different conditions, some of which are sufficiently common to have acquired popular names, such as "muscular rheumatism," "lumbago," and "stiff-neck." The advance of knowledge will no doubt enable us to classify these affections under their proper etiological headings, and to limit the term myalgia to a neuralgia of the sensory nerves of muscle. Such sensory nerves, having as end-organs the familiar muscle spindles, are now well known, and there is reason to believe that they subserve common sensation as well as the muscular sense. But the conveyance of the former is probably effected to a far greater extent by the afferent nerves of the fibrous structures associated with the muscle substance, which in itself is, like all "parenchymatous tissue," comparatively insensitive to pain.

Pathology.—In the absence of evidence from the side of morbid anatomy, our knowledge as to the pathology of myalgia is derived from the conditions with which it is associated, and from the effects of treatment. We must, in the first place, recognise that a small number of cases can be traced to actual inflammation of muscles and their envelopes. Of this two forms at least are recognised, polymyositis and neuromyositis. The former may be acute or subacute; its symmetry and local distribution suggest an

etiological likeness to polyneuritis. Neuromyositis appears, according to Sir W. Gowers, who was the first to describe it, to be of "rheumatic" origin. Apart from these the main predisposing causes of myalgia are gouty, neurotic, and rheumatic; the enumeration of these is sufficient to predicate a marked hereditary tendency. Many cases own a direct excitant in the form of chill or strain, which usually suffices to determine the locality affected. In this connection mention should be made of the myalgic pain following upon the sudden and violent use of "untrained" muscles. Common seats of this form of myalgia are the adductors in horsemen, and the deltoids and pectorals in bowlers; after a few days' practice in either case the trouble does not recur. The pathogenesis of the different varieties of myalgia will be considered along with their description.

Symptoms.—*Muscular pain* is common to all forms; its characters are sufficiently well marked to be of diagnostic value. It is, as a rule, slight while the part is at rest, but becomes acute and at times lancinating on movement. It is not throbbing like that of neuralgia, nor does it become worse at night; it is in most cases relieved by pressure. Its quality varies to some extent with its situation; in the neck it is usually sharp, while in the loins it more often takes the form of a dull persistent ache. In any case it remains localised to the affected part, and does not exhibit the vagaries of neuralgia, the pain of which is often "referred" in such a way as to direct the attention to a spot far removed from the seat of the disease.

Muscular tenderness is also practically always present; on palpation the muscle feels as if bruised. There are no tender spots as in neuralgia.

Muscular spasm is seen chiefly when the neck is affected; its effect is evidently to keep the parts rigid and at rest.

These symptoms usually remain localised in the region first attacked, which is very often the part which has actually been strained or exposed to cold or wet; but in chronic cases they may fly from one muscle group to another, apparently at random. General symptoms are slight and often absent; there may, however, be a feeling of malaise, and there is sometimes a trifling rise of temperature. The onset is almost always acute, or even sudden, but the duration, though commonly short, is very variable.

Varieties.—The following are the principal affections to which the name myalgia has been more or less accurately applied.

SPASMODIC TORTICOLLIS.—This form of wryneck almost always

results from chill. It is commonest in rheumatic subjects, and not infrequently forms a term in the "rheumatic series" of childhood. In this condition the fibrous planes of the neck are far more affected than the muscles, which merely contract in order to relieve tension in the connective tissue beneath, forming, as it were, a natural splint. Were the torticollis due to a pure myalgia, muscular contraction would add to instead of averting the pain.

INTERCOSTAL MYALGIA.—The intercostal muscles are frequently the seat of myalgia, which is often misnamed intercostal neuralgia. The latter is a much rarer affection, is paroxysmal in character, and is associated with tender spots but not with muscular tenderness. The commonest cause of myalgia in this situation is the strain of repeated and prolonged paroxysms of cough, as in phthisis and particularly chronic bronchitis; the lower spaces are the most frequently affected. In this connection two other terms require mention, "pleurodynia" and "mastodynia." The former is a loose expression covering all forms of non-pleuritic pain in the side, without regard to their pathological differences; the latter refers to a form of pain in the upper intercostal spaces, more often on the left side, which is sometimes seen in anæmic women, particularly after prolonged lactation, and is probably neuralgic in origin.

LUMBAGO.—Our knowledge as to the etiology of this common affection is still incomplete, but there can be little doubt that it comprises several more or less closely-allied conditions, involving the back muscles, their sheaths and fasciæ, or both. As regards frequency, the preponderant causative factor is undoubtedly gout. Lumbago often precedes an attack of sciatica in a gouty subject, and may sometimes replace or alternate with arthritic manifestations. It is perhaps more often attended with general symptoms than any other form of myalgia. It is unquestionably more common in men than women, and usually occurs in adult life. The pain of chronic lumbago is generally slight or absent while the patient is at rest; upon exertion it becomes more or less acute, but in many cases, if the use of the muscles is continued, it again abates.

Other muscle groups, such as those of the shoulder and limbs, are less often affected. The angle of the scapula is frequently the centre of a pain which is in part at least myalgic, seeing that it is often associated with tenderness in the serrati. Like lumbago it afflicts chiefly gouty subjects.

Summing up the facts, one can hardly fail to be struck with

the frequency of the gouty factor in myalgia ; rheumatism, on the other hand, appears to be of comparatively slight importance except when the brunt of the affection falls upon the fibrous tissues. It is hardly going too far to say that the expression "muscular rheumatism" is made up of two terms which approach mutual incompatibility ; the sole muscular complaint of which the rheumatic origin is unquestionable is the above-mentioned acute neuro-myositis.

Diagnosis.—This is often attended with extreme difficulty, slight cases being sometimes almost indistinguishable from neuralgia. Well-marked myalgia is, however, readily differentiated by the character of the pain, the absence of tender spots, and the presence of muscular tenderness ; attention has already been called to the fact that the pain is increased by movement, and as a rule relieved by pressure. The pains attending the onset of influenza closely resemble those of myalgia, but there is not as a rule much muscle tenderness, while the temperature is higher than in simple myalgia. The occurrence of a true influenzal myalgia must, however, be admitted. The recognition of the local varieties of myalgia often implies, besides the considerations already detailed, the exclusion of a number of other conditions. Thus the intercostal form may be confounded with pleurisy, with intercostal neuralgia and with pain referred from spinal disease ; a careful physical examination should suffice for diagnosis in each of these cases. The most difficult problem perhaps is to distinguish it from the neuritic pain which precedes the appearance of herpetic vesicles ; the obscurity is, however, soon cleared up by the course of the disease. Diagnostic errors in connection with lumbago are far more important, for many grave diseases are from time to time allowed to masquerade under the cloak of this popular expression. Pain in the back is an early indication of some of the acute specifics, such as small-pox and glanders ; in such cases tenderness is absent, the pain is but little increased by movement, and the temperature, if not as yet very high, is at least suspiciously elevated. Lumbo-abdominal neuralgia is somewhat rare, and is characterised by tender spots in the iliac and hypogastric regions. The various forms of renal pain may be diagnosed by examination of the urine. I have, however, seen a case of perinephric abscess which exactly simulated an attack of lumbago followed by sciatica until the temperature was taken and the abdomen examined. Other conditions which may require exclusion before the diagnosis of lumbago is made are aortic aneurysm, particularly when situate at the level of the

diaphragm, constipation, and diseases of the spine and female pelvic organs. To put it briefly, in a case of pain in the back lumbago should be the last, instead of, as it generally is, the first explanation to be considered.

Treatment. — Patients who are subject to myalgia should obviously avoid exposure to chill, particularly damp cold, and should exercise care in the matter of muscular exertion. They should be warmly clad, preferably in flannel, and a woollen “cholera belt” is to be recommended to those who are liable to lumbago. Seeing that so few cases are truly rheumatic in origin, it is not surprising that salicylates are seldom of much use in treatment; sometimes, however, particularly in torticollis and occasionally in lumbago, they rapidly relieve the pain. In chronic cases alkaline mixtures containing guaiacum and iodide of potassium give most relief; the administration of strychnine, of quinine, and of sulphur has also been recommended by various authorities. A large number of myalgic patients improve greatly under the dietetic and therapeutic regimen appropriate to the uric acid diathesis. But in the great majority of cases immediate benefit is derived from local treatment. In a large proportion the pain is at once assuaged by belladonna fomentation; if this fails, a blister will almost invariably give relief. Liniments are of most use when the trouble is mild but persistent; chloroform and belladonna form an excellent combination. The use of morphia is seldom necessary or advisable. Many cases of lumbago may be promptly cured by thrusting a sterilised needle deeply into the affected muscles and leaving it there for five or ten minutes. The application of hot air by the Greville method is also of great service, particularly in chronic cases, and benefit may likewise be obtained from mild galvanic currents, the positive pole being applied over the seat of pain. The saline baths of Droitwich and Llandrindod have many advocates, but as regards the combination of baths with suitable climatic conditions no English resort is better adapted to the cure of myalgia than Leamington.

BERTRAM ABRAHAMS.

MYOSITIS OSSIFICANS

This is an affection of early life characterised by local inflammatory changes in the muscles followed by ossification. Only about sixty cases have been recorded since the disease was first described by Freke in 1740. In about 25 per cent the symptoms appeared during the first year of life, and in nearly 85 per cent below the age of fifteen; the male sex is more frequently affected than the female in the proportion of five to two.

The **etiology** is unknown, but it has been plausibly suggested that there may be a congenital tendency to ossification in the muscles on, so to speak, slight provocation. Certain it is that 60 per cent of the patients show the curious, and otherwise rare, deformity known as microdactyly. Of exciting causes by far the commonest is injury, which is usually quite definite though often very slight. It is only in a small proportion of cases that trauma can be excluded; in a few of these the complaint has followed a severe chill. It is probable that most of the instances recorded in the first year of life derive from injury at birth.

The **anatomical changes** consist in ossification of the inter- and intra-muscular connective tissue. There has been much discussion as to whether the process is by nature inflammatory or akin to the formation of a new growth. Recent investigations point to its commencement in an acute or subacute myositis, and the former view is hence now generally adopted.

Symptoms.—Almost always the first symptoms are those of a local acute myositis. There is a doughy swelling in the affected muscle, with pain, cedema, and slight fever. These subside in a few days with the exception of the swelling, which persists and hardens. After a varying interval another attack supervenes, and this is repeated with more or less frequency; very often each successive attack is induced by a fresh injury. Eventually the whole musculature, with certain exceptions, may be converted into branching masses of bone. The muscles of the neck and back are most frequently and extensively affected; it is very rare for the latter to escape. Later on the limbs are attacked and contractures produced. The masseters and temporal muscles are often involved, giving rise to great difficulty in feeding. The sphincters, tongue, diaphragm, and muscles of expression escape, as also do those of

the perineum. The ossification is accompanied by a muscular atrophy which exceeds that which could be accounted for as the result of disease. The most common complication is, as has already been mentioned, microdactyly, usually affecting both thumbs and great toes. General symptoms are absent, except that amenorrhœa is very common.

The course of myositis ossificans may be described as jerkily progressive. The onset is followed by a period of quiescence, which gives place to more or less frequent repetitions; the whole has been well characterised as a "chain of local affections." Death may occur from an accident caused by the helplessness of the patient, or by pyæmia starting in suppuration round the new masses of bone, but in most cases it is the result of some inter-current affection, particularly of the lungs.

The **diagnosis** presents no difficulties; the curious crouching attitude of the patient is itself in a young subject characteristic.

Treatment.—Nothing is known which can affect the process of ossification. The chief indication is watchful care to avoid trauma; the subject of myositis ossificans requires almost as much looking after as the hæmatophil. During the acute phases iodine may be rubbed in with advantage. Surgical interference may be needed when feeding is interfered with; otherwise it is worse than useless, as new bone is sure to form in the scar tissue.

LOCAL INTRAMUSCULAR OSSIFICATION.—This is a not infrequent result of trauma, either spontaneous rupture or severe external injury on the one hand, or on the other repeated slight damage. The latter cause is often seen in the adductor muscles of horsemen ("rider's sprain"). The bone arises after chronic inflammation in the connective tissue; in severe injuries blood-clot is also present as a basis. The affection is not progressive.

BERTRAM ABRAHAM.

RICKETS

This is by far the most frequent disease of infancy and early childhood. Any reliable estimate as to its relative frequency is unobtainable owing to the varying opinions of different observers as to the amount of departure from the normal state that is necessary to justify the diagnosis of rickets. Some authorities have gone so far as to declare that some degree of rickets, slight or severe, is the portion of every hand-fed infant, whether town or country bred. Others again regard almost every town-bred infant, whether hand-fed or suckled, as being of necessity more or less rachitic. Even without the inclusion of doubtful cases, dependent for their diagnosis on the individual bias of the observer, rickets still remains the most frequent complaint of infancy.

Age of onset.—From the extremely gradual development of the symptoms, this is difficult or impossible to fix with any precision. Any definite characteristic symptom, such as beading of the ribs, is seldom, however, observed before the age of three months. It is very seldom, too, that any increase of the epiphyseal enlargements takes place after the age of two years. These two ages may, perhaps, be taken, with approximate accuracy, as the limits between which the disease manifests itself for the first time. That symptoms first appear in the second half of the first year of life in the vast majority of cases is incontestable. It is equally certain, however, that unmistakable rickets is not infrequently seen in infants under the age of six months, and also that in very numerous instances no symptom of the complaint has been present before the second year of life.

Sex.—For some reason; not easily explainable, rickets is more frequent in male than in female infants. The proportion of males to females affected is certainly not less than that of five to four, whilst some observers would place it nearly as high as that of three to two.

Etiology.—That rickets is infinitely more prevalent proportionally amongst hand-fed infants is beyond dispute. That the complaint, too, can originate from the use of a diet in which all the necessary ingredients are habitually deficient would be as readily conceded by all. Whilst this is the case, different observers have claimed an exclusive origin for the complaint in the deficiency of

one separate ingredient only in the food, such as a lack of fat, or of proteid material, or of the lime salts. At least one eminent authority has stated that breast-fed infants never acquire rickets. So far is this from being the case that numerous infants contract rickets in the early months of life whilst still at the breast. More than this, it is possible that the most pronounced examples of the affections of the bones in rickets occur in infants that have been too long suckled, or where the mother's milk has been replaced, after weaning, by a diet too exclusively farinaceous in character. It has been pointed out by some authorities that excessive bony changes in rickets almost necessarily imply a previous state of good nutrition on the part of the infant to admit of their development. Some writers would seem to wish to acquit the diet from any charge of the production of rickets, and lay the chief blame on the bad hygienic conditions under which most of the children are brought up, and especially on the absence of exposure of the infant to the influence of bright sunshine. Possibly there is a germ of truth in all these theories, and many factors may have a share in the production of the complaint. Broadly speaking, rickets is a disease of malnutrition, however that malnutrition may be brought about. Thus it may be induced in a healthy infant by a diet deficient in all the essential ingredients, or by one in which a single ingredient only is at fault; and this whether the infant be suckled or hand-fed. The complaint, too, may readily develop in infants fed on a diet exemplary in every way, but where, owing to unhealthy sanitary surroundings, or to some inherent defect in the infants themselves, they are unable to satisfactorily digest the appropriate diet. Again, rickets may be induced in an infant by the effects left by some other disorder, such as chronic diarrhoea or inherited syphilis. Very few of the survivors from the last complaint, indeed, escape from definite rickets in the later months of infancy. Whilst this is undoubtedly true, the opinion formerly held by Parrot that rickets is merely a modification of inherited syphilis is fallacious and altogether untenable.

Pathology.—This is mainly concerned with the changes from the normal in the development of the bones, and has been summed up in the statement that in rickets there is an exaggerated preparation for ossification with defective performance. At the junctions of the epiphyses with the shafts of the bones there is an enormous increase in the zone of multiplication of the cartilage cells. The groups of cells are in much greater numbers, and not only occupy a greater space, but have lost the normal arrangement in rows parallel to the long axes of the bones. The cartilage cells, too, vary

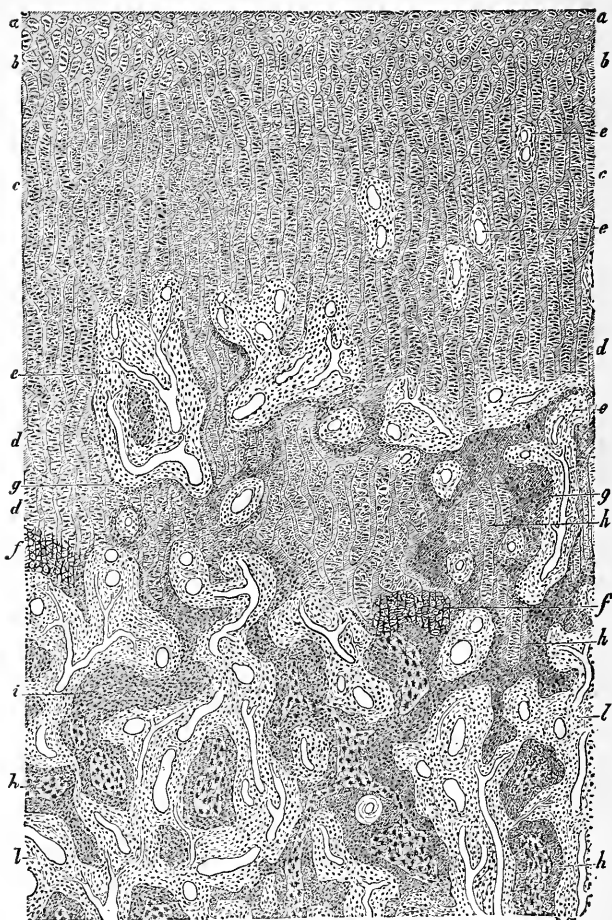


FIG 20.—Longitudinal section through the line of ossification of the upper end of the diaphysis of the femur of a one-year-old child, suffering from rickets of moderate severity; $\times 50$. *a*, unaltered hyaline cartilage; *b*, cartilage in the first stage of proliferation; *c*, zone of columns of proliferous cartilage cells; *d*, columns of proliferous hypertrophic cells; *e*, vascular medullary spaces within the cartilage; *f*, calcified cartilage; *g*, osteoid tissue; *h*, remnants of cartilage amid osteoid tissue; *i*, trabeculae of osteoid tissue devoid of calcium salts; *j*, trabeculae formed of osteoid and completely ossified tissue; *l*, vascular fibro-cellular medulla. (From Ziegler's *Pathological Anatomy*.)

considerably in size. The calcification of the zone of the cartilaginous matrix proceeds in the most irregular fashion. There may be calcification of the cartilage above, whilst lower down groups of cells remain uncalcified. The formation of medullary cavities and development of bone are also abnormal. Blood-vessels appear with considerable frequency in the midst of the cartilage, and medullary spaces may be present in the deeper parts with osteoblasts in them. But the medullary cavities do not occur with any greater regularity than the rest of the processes, and it is not always clear that they are concerned with bone formation.

The coarse result of these changes is enlargement of the epiphyseal ends of the bones, along with undue softness and vascularity. On longitudinal section of a bone the blue zone is seen to be greatly increased and its boundaries irregular. The yellow zone of calcification is still more irregular, and yellow patches may appear in the midst of the blue zone.

The changes in the shafts of the bones consist in an increase of the usual thin layer of osteoblasts under the periosteum. Instead of a proper dense bone being formed on the surface of the shaft, there is a loose irregular spongy bone with ill-formed trabeculæ. The lime salts, too, are deposited without combining with the bony matrix in the usual manner, and the process is one of calcification rather than an ossification. The chief naked-eye characters of this consist in an increased vascularity of the sub-periosteal layer, whilst the shaft is thicker than normal and more easily bent.

The after-effect of these pathological changes is that the outer layers of the long bones become unusually dense and hard. A similar sclerotic change is stated by some authorities to occur in the cranial bones as the result of rickets.

Symptoms.—The effect of rickets are so numerous and varied that it is difficult to deal with them in any systematic or regular order. For the sake of convenience, then, it is proposed to take the principal regions of the body separately, and after first describing the changes in the bones, to proceed directly to the consideration of any affection occurring in the adjacent or contained organs.

In the *skull* the most constant rachitic affection is the undue patency of the anterior fontanelle. In healthy infants this is generally closed about the age of eighteen months, but in rickety children it may remain open until the age of five or six years. When the anterior fontanelle is very large, a patent interfrontal suture can in many cases be traced from its anterior margin down almost to the

root of the nose. When this is the case the remaining sutures are always patent as well. Along the margins of each suture, and around those of the anterior fontanelle, slight, but distinct, thickening of the adjacent bones can be felt. For some time after the sutures are closed their former situations can often be traced by the elevated ridges at the edges of the bones resulting from this thickening.

Craniotabes, of the same character and in the same situations as in inherited syphilis, is not uncommon in the earlier stages of rickets. A fairly constant feature is some degree of thickening and elevation of the frontal and parietal eminences, parts seldom if ever involved in inherited syphilis. Any excessive elevation of the frontal and parietal eminences leads to what may be regarded as the typical rachitic skull, one with a broad, square, prominent forehead, and unduly flat on the vertex. Such a type of skull is frequently, but erroneously, entitled "hydrocephalic." Such an error should not arise, for, among other distinctions, whilst the vertex of the rachitic skull is unduly flat, that of the hydrocephalic one is unduly elevated and convex. Occasionally, owing to pressure over the softened bones, the rachitic skull is asymmetrical in shape; the commonest deformity here being flattening in one occipital region, with a corresponding bulging over the frontal region on the same side. The bones of the jaws are sometimes affected, becoming what has been termed "beak-shaped" in character, owing to flattening at their sides, causing undue prominence and narrowing of the parts in front. The deformities of the skull may persist throughout life, and it is possible amongst adults to select out those who have been rachitic in infancy from the contrast presented between the broad prominent forehead and the shrunken chin.

The *teeth* are generally late in appearing, are prone to decay early, and in some cases where long delayed have been described as being already decayed on making their first appearance through the gums.

The commonest affection of the *thorax* is the beading of the ribs at their junctions with the cartilages. This beading is seldom absent, and as a symptom may precede all others. It is most marked about the sixth and seventh ribs, and the beads can be seen and felt symmetrically on both sides of the chest, forming what is known as the "rickety rosary." In some cases the beading is more developed on the pleural than on the external surface of the ribs. In very severe cases nodular thickenings may form at the posterior angles of the ribs; these are due to callus formed over the sites of green-stick fractures. Just exterior to the "rickety rosary," on both sides, is often a broad, shallow groove, extending from the upper

and anterior part of the axilla downwards and outwards as far as the seventh rib. In addition to this there may be a transverse groove, "Harrison's sulcus," commencing at the ensiform cartilage and disappearing gradually near the middle of each axilla. Each of these grooves is markedly deepened and accentuated on inspiration whenever there is any respiratory trouble. When the longitudinal grooves are well marked the costal cartilages form an obtuse angle with the ribs, and thus come forward, thrusting the sternum along in front of them. The prominent sternum in advance of the chest and the two grooves form the rachitic variety of pigeon breast. The chest under such conditions is roughly violin-shaped in transverse section.

Corresponding roughly with the line of beads on the ribs, there is often a band of collapse of the lung on both sides of the body. The thin edges of the *lungs*, anterior to these bands of collapse, may be markedly emphysematous. In addition to possibly suffering from troubles arising directly from the last-named physical conditions, rickety children are specially prone to pulmonary catarrh and bronchitis. These last, owing to the ineffectual inspiratory efforts on the part of the infant, consequent on enfeebled muscles and softened ribs, often lead to extensive collapse of the lung and broncho-pneumonia, two of the most fatal complications of rickets. The diminution in the size of the thorax leads to relative displacement of the heart with regard to the chest wall, and, although the heart is not enlarged, the apex beat may be well outside the nipple. In rare instances a white thickening of the pericardium, "milk-spot," may be found post-mortem, corresponding to the place of impact of the heart against the chest wall.

Rickety *curvature of the spine* is so common that it has furnished the name to the complaint (*ρᾶχις*, a spine). Here the normal curves are replaced by a single one, convex backwards, commencing near the first dorsal vertebra and terminating over the sacrum. This affection is sometimes mistaken for Pott's disease, but it can be distinguished from the last by the following criteria. The rachitic curvature is a perfectly gradual one, it is free from any angularity or sharp projection and unaccompanied by pain, and it entirely disappears when the infant is lifted up by the axilla and traction is made upon the legs. It is due to muscular weakness rather than to any rachitic changes in the vertebræ or their cartilages.

The *abdomen* is always enlarged, and "big belly" is not infrequently the first symptom that attracts the attention of the mother to the state of the child. The enlargement may be due partly to diminution in size of the thorax and pelvis, assisted by enlargement

of the liver and spleen, but is chiefly accounted for by the flabby abdominal walls yielding to the pressure of intestines distended with flatus.

The *affections of the pelvis* consist in thickening of some of the bones with narrowing of the pubic arch; or there may be a wide sub-pubic angle with a short antero-posterior diameter of the brim—the “reniform pelvis.” They are of interest mainly to obstetricians, as the deformities resulting from them may lead to difficulties in parturition in adult life.

In the *limbs* the most frequent and noticeable rachitic feature is the enlargement of the epiphyseal ends of the long bones. At first confined to the line of junction between the epiphysis and the shaft, the enlargement soon involves the epiphysis as a whole. In the upper limb the epiphyseal swellings are most prominent in the lower ends of the radius and ulna, but they can be found to a less degree in the upper ends of these bones and in the lower end of the humerus. In the lower limb the lower end of the tibia is most markedly affected, and after this the upper end of the tibia and the lower end of the femur in the order named. The epiphyseal enlargements usually subside during the third year of life, but may persist until the age of five years or later.

The *ligaments* suffer in nutrition with the rest of the body and become unduly lax, and this, coupled with the attendant muscular weakness, admits of considerably freer movements in the joints than is possible in health.

During the active stage of the complaint the *muscles* are invariably flabby on palpation, however well nourished and even fat the infant may appear to superficial examination. In some cases the muscles are demonstrably thin and ill-developed. Where muscular weakness is extreme, this is possibly as much due to the associated mental backwardness as to the mere physical condition of the muscles themselves.

Deformities arising from bending of the shafts of the long bones are far from a necessary consequence of the disease, and only occur in a minority of cases. The deformities are usually exaggerations of the normal curves of the bones, and may proceed to a marked degree before walking or other exercise has had any share in their production. There is no doubt, however, that the deformities of the legs can be vastly increased by walking, and those of the arms by the infant partly supporting its weight by pressure applied through the palms of the hands. In the lower limbs the commonest deformity is the well-known “bow-legs,” but “knock-knee” is not

infrequent. In the upper limbs the most frequent deformities are outward bending of the humerus, or bowing of the radius and ulna with the convexity towards the posterior surface. In the clavicles, by the insertions of the sterno-mastoids, it is not very unusual to find symmetrical bony thickenings; these are the results of green-stick fractures of these bones. Such fractures occasionally occur in other bones, without any noticeable violence to account for them, and attention may first be called to them by the resulting callus, or by some more decided deformity.

The active stage of the bone changes in the limbs is seldom, if ever, attended by any marked *pain*. Some authorities, however, have stated that, owing to stretching of the pericranium, the bone affections of the skull are accompanied by pain, and that this last is manifested by rolling of the head. This rolling of the head, more especially if any ear trouble be present, may lead to thinning and rubbing off of the hair over the occipital region. Any marked pain in the regions of the larger joints is probably of scorbutic rather than of rachitic origin.

Of the general symptoms, *head-sweating* is the most frequent, indeed it may be said to be invariably present. It is always an early symptom, and may usher in all others. Although most marked about the head, profuse sweating is usual over the rest of the body. When the perspiration is marked about the body, the skin is usually coarse and muddy-looking, and the superficial veins unduly prominent.

Pyrexia is described by some authorities as accompanying the active epiphyseal and bone developments. If so, it is under these circumstances an extremely evanescent phenomenon, and pyrexia, in the vast majority of instances, is due to some pulmonary, intestinal, or other complication.

Restlessness is a common phase of the disease, and is manifested by the distaste shown by the infant for covering of any sort. Both by night and by day the rachitic infant has a tendency to throw off the bed-clothes, whether the weather be that of mid-summer or the depth of winter.

A certain degree of *anæmia* is usually present in most cases. If the anæmia is extreme, the spleen should be examined and will often be found enlarged. In some cases, usually those where anæmia is marked, a bruit arising in the venous sinuses of the brain may be heard on applying a stethoscope to the sides or back of the skull. Such bruits are, however, often audible when neither anæmia nor rickets is present, and are of no particular clinical

significance or import. The inexperienced are very prone to diagnose cerebral aneurysm from the presence of such bruits alone, but such a complaint as cerebral aneurysm is, needless to say, unknown in infancy.

Much has been made by some writers of *enlargement of the liver and spleen* in rickets. It is only in exceptional cases, however, that any enlargement of either of them takes place. As in other complaints of infancy, the presence of enlargement of the liver, without it be excessive, is difficult to pronounce upon with any degree of precision. In any case, enlargement of the liver in rickets is of no known practical import, and is seldom of any clinical prominence.

Enlargement of the spleen does not occur certainly in more than 5 per cent of all cases. In exceptional cases the enlargement may be of considerable extent, and is then often associated with a diminution of the number of the red blood corpuscles, but no increase of that of the white in the infants affected. In the great majority of cases the enlargement starts in the second year of life, and very seldom lasts beyond the end of the third year. There is no need to assume any association of syphilis with rickets, when the spleen is enlarged in the last complaint, as some authorities have suggested.

Diarrhœa is frequent in rickety children, and is apt to be exceedingly persistent and chronic. In some infants diarrhœa and troublesome constipation alternate with each other. Whether diarrhœa be present or not the motions are seldom healthy in character. They may be white, green, or brown in colour, with or without frothy mucus, and are usually characterised by their foul stench.

An infant with rickets is often mentally backward, and is usually much later in walking and talking than a healthy child. The backwardness in walking, as has been before stated, is much more pronounced than the local state of the muscles themselves would account for, and is then partly dependent on the associated brain state. When walking is long delayed, a suspicion that the child is paralysed is apt to arise in the parents' minds, and in the majority of infants brought to children's hospitals for paralysis, rickets is found to be the sole disorder.

The frequent and close connection between *convulsions* and rickets in infancy is now universally recognised and admitted. In some instances the immediate exciting cause of the convulsions is to be found in dentition, intestinal or pulmonary disorder, or the advent of some acute disease. More often, however, the convulsions happen without the discovery of any immediate exciting cause.

Although frequent in the disorder, the mere fact of an infant suffering from convulsions is no proof of its being rachitic.

Still more closely associated with rickets than even convulsions are *laryngismus stridulus* and *tetany*. The first, commonly known amongst mothers as "child-crowing," is dependent upon spasm, more or less sudden, of the adductor muscles of the larynx. After several short whistling inspirations the breathing suddenly ceases and the infant may appear at the verge of suffocation, and in fact may actually die during the attack. Usually, however, the spasm relaxes and the air is redrawn through the larynx with the loud characteristic inspiratory crow. Tetany is a peculiar affection characterised by painful, tonic contractions of certain groups of muscles. The spasm may affect the muscles of the neck and trunk, but it is mainly those of the limbs and especially of the hands and feet, carpo-pedal contractions, that give the distinctive features to the complaint. In the upper limb the hand is flexed at the wrist, the thumb drawn in upon the palm of the hand, whilst the fingers are drawn together, flexed at the metacarpo-phalangeal joints and extended at the others, and bent over the inturned thumb. In the lower limb, the foot is extended upon the leg by the drawing up of the heel, the dorsum is unduly arched, and the big toe is covered by the rest, which are drawn together and flexed over it. The painful spasms may last a few minutes, or many hours or even days.

These last two affections are very rarely found in infancy dissociated from rickets. The three disorders, laryngismus, tetany, and convulsions, often occur at different times in the same infant. Indeed, attacks are not infrequent in some infants when all three occur, either almost simultaneously or without any appreciable interval between the times of their manifestations.

For the first recognition of the association of most of these nervous disorders with rickets, we are indebted to the late Sir William Jenner. An explanation of their occurrence, and of many of the general symptoms as well, is perhaps to be found in the fact that in rickets the brain suffers proportionally with the rest of the body in the general malnutrition.

One of the rarer nervous manifestations usually, though not necessarily, associated with rickets is that in which there is a combination of *nystagmus* and certain movements of the head. The latter generally consist of a jerking from side to side with an occasional vertical nod; less commonly they are mainly vertical in character (*spasmus nutans*). The movements cease when the infant is lying down or asleep. The *head-jerking* is accompanied by

nystagmus, which is most frequently horizontal, but may be rotatory or vertical. The nystagmus may be entirely confined to one eye, and is usually more marked on one side than the other. It is increased in intensity when restraint is placed upon the movements of the head. The affection generally commences during the second six months of life, but may begin as early as the second month. Occasionally the nystagmus appears alone and precedes the movements of the head by weeks or several months. The condition lasts a variable time, from a few weeks to many months. A usual time for its disappearance is about the end of the first year, but it may continue until the completion of the first dentition. Recovery from both the head movements and nystagmus is always complete. This temporary affection must not be confounded with that in which more extensive bowing, or swaying of the whole body from the hips, occurs (mandarin or salaam spasm), as this last is usually, if not always, associated with grave congenital mental deficiency.

Two other disorders have been by many so closely associated with rickets, that they may be briefly described here.

LATE RICKETS. — Occasionally marked enlargement of the epiphyses, and somewhat rapid bending of the limbs, occurs in older children, usually at, or soon after, the commencement of the second dentition. Beyond the bony changes, however, these cases of so-called "late rickets," or "rachitis tarda," present none of the usual signs of the infantile complaint. Whatever may be its nature, the disorder is specially prone to occur soon after the incurrence of some weakening disease. The pathology of such cases is obscure, and the prevalent view, that they are examples of a recrudescence of a rickets contracted in infancy, is far from proven. Cases of "late rickets" are exceedingly rare. They have been observed as early as the age of four years, and as late as that of seventeen.

ACHONDROPLASIA. — This is a rare disease, which has been variously described as foetal, or intra-uterine, rickets, and as foetal cretinism. At the present day, however, it is not considered to have any real connection with rickets. The subjects of achondroplasia are born with certain deformities which persist throughout life. The head is relatively large, the chest narrow, and the limbs only about half the normal size. Although all the bones of the limbs are developed, the chief diminution in size occurs in the femora and humeri, so that the thighs and upper arms are shorter than the legs and forearms respectively. The nose is markedly "pug-shaped," with a depression at the root, and the tongue is usually protruded from the mouth. Such children are usually

premature, and the majority either still-born or die soon after birth. In the survivors there is a tendency to rickets at the usual age for that disorder.

ACUTE RICKETS.—Cases that were formerly described under this heading are now more accurately recognised as infantile scurvy. The onset of true rickets, it may be said, is always gradual and never acute.

Diagnosis.—In well-marked cases this offers no difficulty. The shape of the skull, with the undue patency of the fontanelles the enlargement of the epiphyseal ends of the long bones, the beading of the ribs, the delayed dentition, along with such symptoms as head-sweating, muscular weakness, and mental backwardness present a clinical picture absolutely characteristic of the complaint. In other cases, however, it may be a matter of impossibility to say whether the symptoms present could accurately be classed as rachitic, so slight being the changes from perfect health, and so gradually do the processes normal to childhood pass into those that are pathognomic of rickets. Such slight cases, however, are generally of no clinical or practical import. It is the bone lesions, of course, that clinch the diagnosis in the vast majority of instances. But in some cases other symptoms may precede the skeletal changes, and, again, in other cases of some long duration certain symptoms may, perhaps, authorise the diagnosis of rickets, where the bony changes are so slight as to be almost inappreciable. Thus head-sweating, so constant a feature in most cases, may precede any bony changes, or other symptoms, by many months. In children, too, where no tooth has been cut at the age of ten months, there is a strong probability that rickets is impending, and where dentition is delayed for a year, the advent of rickets can be predicted with a large degree of certainty. Laryngismus stridulus, again, is so closely associated with rickets that some eminent authorities do not hesitate to diagnose the last complaint whenever the former symptom is present. Other observers, however, have met with a few cases of laryngismus stridulus where rickets could with certainty be excluded. Whilst, then, the occurrence of laryngismus stridulus in an infant is strong presumptive evidence of its being rachitic, the dogmatic assertion by some authors that every case of laryngismus is one also of rickets would seem to go too far. What has been said about laryngismus stridulus applies equally to tetany, and also, but to a much less degree, to convulsions in infants. All that can be claimed with any exactness for the diagnosis of rickets, from the mere presence of these nervous disorders alone, is perhaps the following—if laryn-

gismus or tetany occur in a child who has been brought up under the conditions usually leading to rickets, then their mere presence is almost convincing proof of rickets, although the bony evidences of the latter complaint may be of the very slightest.

Prognosis.—Rickets is probably never fatal *per se*, but is, nevertheless, indirectly accountable for the deaths of many victims by means of its complications. For one of its very fatal complications, broncho-pneumonia, rickets itself may be directly responsible owing to the weakened inspiratory efforts leading to pulmonary collapse. Diarrhœa, too, is more frequent and more fatal in rickety children than in others. Rickety children, again, are probably less able to resist the invasion of most diseases, and are certainly less able to recover from them than the more robust. Indirectly, then, rickets is responsible for far more numerous deaths than the ordinary mortality returns would credit it. Apart from complications, the prognosis is good. If the distortions of the limbs have not proceeded to too great a degree, they are usually thoroughly recovered from in the course of time, and the vast majority of persons who have been rachitic in infancy present no traces of their former complaint in adult age. The deformities of the limbs may, however, persist throughout life, and the curvature of the legs lead to considerable diminution in stature. In other cases, apart from any bending, the limbs may be permanently dwarfed owing to the damage at the junctions of the shafts and epiphyses interfering with the proper development of the long bones. Sir William Gowers, however, claims that 10 per cent of adult epileptics derive their complaint from convulsions arising from rickets in infancy. Other authorities, too, have asserted that not only epilepsy, but migraine, asthma, chorea, and other nervous disorders have their origin in a past rickets. It has been suggested that these disorders have arisen from the damage inflicted on the growing nervous system, at a period of its greatest developmental activity, by the malnutrition in which the brain and spinal cord share with the rest of the body in rickets. If this be true, the importance of rickets in infancy is far more extended than is commonly ascribed.

Treatment.—The first essential in the treatment of rickets is strict attention to the diet of the patient. The meals should be given at regular hours, and should contain a due amount of fat and proteids. A very common fault in the dietary of such patients is that the meals are deficient of a proper proportion of the former ingredient. Rickety children, as a rule, are fond of fat, and will

digest a much greater amount of it than is ordinarily given. An excess of it, however, more than the child can digest, may give rise to vomiting, whilst too much proteid aliment may occasion diarrhœa. In colder weather the fatty ingredients in the food may be supplemented with advantage by twenty or thirty drop doses of cod-liver oil. In the summer, and when the weather is unduly warm, the last should not be given. At such times oil usually does far more harm than good by upsetting the digestive organs, and often starts an attack of diarrhœa and vomiting which may even prove fatal.

At the same time as regulating the diet, attention should be paid to the proper ventilation of the living and sleeping apartments. A rickety child can scarcely have too much out-of-door air or sunshine. Many cases, too, that in towns, and even in the country, fail to improve, make marvellous progress on a temporary change being made to seaside air.

In the evening the child should have a bath, and in the morning should be rapidly sponged all over with luke-warm water ; or the times of bathing and sponging can be reversed. A serious objection to the bath, as usually given, is the length of time it occupies. Now rickety children, even more than others, should be protected from any prolonged chilling of the body surface. It should be pointed out to mothers that a much less elaborate and prolonged function than the usual bath is desirable, and will meet all the requirements of the case. After bathing and sponging, the child should be dried with a bath towel, and the body and limbs be briskly rubbed over with the hands. This not only improves the defective circulation, but has a marked effect in increasing the nutrition in other directions. When the head-sweating is profuse, the child's cot should be provided with a hair pillow.

As rickety children are specially prone to bronchitis and pulmonary collapse and diarrhœa, the clothing is of prime importance. This should be of flannel or some other woollen substance, and should fit smoothly and closely over the body, coming well up to the neck and down to the wrists. Woollen stockings coming well above the knees should be worn. A well-fitting flannel binder, evenly applied to the abdomen, is a great protection against diarrhœa and other digestive disturbances, and such a binder should be worn by all children until flannel drawers or some other equivalent can be substituted. With clothing such as that suggested next the skin, there is no need for many of the numerous and elaborate garments in which young children are usually habited. These

usually restrict the desirable free use of the limbs, and interfere with the play of the respiratory muscles, and so foster collapse and other deformities of the chest.

In by far the vast majority of cases splints are unnecessary and even harmful. It has been pointed out that the deformities of the limbs, if any be present, are usually exaggerations of the normal curves, brought about by muscular action rather than by pressure and weight of the body acting on the softened bones. For the correction or prevention of such deformities, then, the rational treatment is that of striving to improve the nutrition of the muscles. For this purpose rubbing and some of the simpler forms of massage are eminently useful, and suffice to cure the vast majority of cases without the use of splints. These last, it has been claimed, by hindering the use of the proper muscles, may actually perpetuate, or even increase, the very trouble for which they are applied. They may certainly impair the general health by preventing exercise, which is even more essential for the child than for the adult. In exceptional cases, however, such as those in which, after the measures already suggested have been tried, the deformities of the limbs steadily increase, splints are advisable, and in those in which there is any suspicion of an antero-posterior bending of the tibia almost a necessity. When splints are applied they should project beyond the limbs so as to prevent locomotion on the part of the child entirely. The child should not be allowed to sleep with them on. After their removal in the evening, and again before applying them in the morning, the limbs should be well rubbed and massaged.

For the treatment of rickets as a general disease no drug is probably of any service. Several eminent authorities have advocated the giving of minute doses of phosphorus dissolved in oil, but it is difficult to imagine of what use such treatment can be. For the anæmia, such a frequent concomitant of rickets, the double citrate of iron and ammonia, given in two grain doses with an equal quantity of citrate of potash, is better than the tincture or any of the other acid preparations of iron. Bromide of potassium or sodium, in two or three grain doses, with or without the addition of a grain of chloral, is the best remedy for laryngismus stridulus, tetany, and the other nervous complications of rickets.

The treatment of any permanent deformities resulting from rickets lies mostly in the province of the surgeon. Dumb-bells and appropriate gymnastic exercises will do much to diminish and improve pigeon breast and other deformities of the chest.

J. A. COURTS.

ACROMEGALY

Although isolated cases presumably of this disease had already from time to time been recorded, it was Pierre Marie who, in 1885, first suggested the name and claimed a definite identity for acromegaly. Commencing usually in adults of from twenty to twenty-five years of age, and rather more commonly in females than in males, the disease, which runs an extremely insidious course, is characterised chiefly by enlargement of the face and of the hands and feet. No evidence is forthcoming as to the causation of acromegaly, and although in some recorded cases there has been a rheumatic or gouty tendency, and in some a history of syphilis, it has not been shown that any causal relation exists between them and acromegaly.

Symptoms.—The alteration in the hands is usually the first symptom which attracts attention. The enlargement concerns chiefly their width and thickness, without, as a rule, any proportionate increase in length. The bones and soft parts are alike involved, but there is no constant increase in the girth of the wrist. In a woman the contrast between the size of the hand and the rest of the upper limb may be particularly striking. The nails are not as a rule much enlarged nor incurved, nor are the terminal phalanges "clubbed." In the feet the changes are in all respects similar to, but usually less marked than, those in the hands.

The changes in the head are very characteristic, and, whilst the cranium suffers little, the face may undergo such profound alterations that the patient becomes quite unrecognisable by his friends. The face becomes long and oval, and there is thickening of the supraciliary ridges and the margins of the orbits, prominence of the cheek bones, and a striking enlargement of the lower jaw, the angle of which becomes more open than natural, so that the lower teeth project beyond the upper. The teeth also may be widely separated. The alteration in the face is still further increased by enlargement of the nose and of the lips, especially the lower. The ears may be similarly affected, the cartilages being thick and rigid, and a frequent symptom is hypertrophy of the tongue, also of the uvula, tonsils, and pillars of the fauces. The skin of the face is often thick and coarse.

Another noticeable and almost constant feature of the disease

is curvature of the spine, which takes the form of kyphosis in the cervico-dorsal region, with a compensatory lordosis in the lower part of the column. All the bones of the chest wall, but especially the sternum, are thickened, and the antero-posterior diameter of the thoracic cavity is increased. The bones of the pelvis also may be thickened, and the external genital organs are often hypertrophied.

The most constant and troublesome subjective symptom of acromegaly is headache. This may indeed be the first symptom, and is often associated with pains in the limbs, which are referred to the bones and joints. As the disease progresses general muscular weakness becomes more and more noticeable, and the patient's mental state more and more depressed. In almost all instances of the disease occurring in women, amenorrhœa has been an early symptom. The appetite is usually good, and there may be considerable thirst. The voice almost always becomes changed, most noticeably in women; it is thick, chiefly as a result of the enlargement of the tongue, and deep, as a result of enlargement of the larynx.

Amongst other symptoms which are occasionally present are shortness of breath, pallor, excessive perspiration, polyuria, glycosuria, and enlargement of the superficial veins, with, in some cases, hæmorrhoids, cardiac hypertrophy, and a systolic apex bruit. The sight is often impaired, bitemporal hemianopsia, and in some instances complete blindness has resulted from neuro-retinitis. The other special senses have in some cases also been affected. A form of insanity with delusions, comparable to that occasionally met with in myxœdema, has been seen.

Diagnosis.—In supporting his claim to regard acromegaly as a definite disease, Marie has very carefully considered the means by which it can be distinguished from those affections which it most nearly resembles. From osteitis deformans acromegaly differs most notably in the enlargement of the face rather than the cranium, and that in the limbs it is the hands and feet and not the long bones which are particularly affected. In osteitis deformans, moreover, the enlarged bones are markedly deformed; the disease is met with usually at a later period of life, and the distribution of the bone lesions are more irregular. From gigantism acromegaly may be readily distinguished by the want of proportion presented by the enlargement of the face and extremities, by the absence of increase in height, and by the onset of the disease in individuals who were previously normally developed. Confusion can hardly arise between acromegaly and the effects of chronic rheumatism, or between it

and leontiasis ossea. The differences between the enlargements caused by acromegaly and those met with in so-called hypertrophic pulmonary osteo-arthritis are referred to in the description of the latter affection. The diagnosis of these several osseous and arthritic changes may be facilitated by examination with the Röntgen rays.

Prognosis.—The course of acromegaly is very chronic and steadily progressive. Year by year the changes increase and the patient becomes more feeble. Death may result from general weakness, or the fatal termination may be hastened by some complication, such as bronchitis. In a few recorded cases the disease has pursued a much more acute course than usual.

Morbid anatomy and pathology.—The most interesting fact in connection with the morbid anatomy of acromegaly is that in almost all the cases which have been examined after death the pituitary body has presented more or less marked evidence of disease. In 1898 Mr. Furnivall was able to collect forty-nine records of post-mortem examination in cases of acromegaly, and in all the pituitary body presented some departure from its normal condition. In forty-seven cases the gland was enlarged, the cause of the enlargement being in some instances a hypertrophy, and in others a tumour, adenomatous, gliomatous, or sarcomatous. In the remaining two cases the pituitary was not enlarged, but in one of these it was the seat of a softened adenoma, and in the other there was necrosis with softening. It is of interest that in all the recorded cases of acute acromegaly a sarcomatous growth has been found in the gland. Enlargement or atrophy of the thyroid gland and persistence of the thymus have also been met with somewhat frequently. The periosteum of the enlarged bones is thickened, and layers of new bone are deposited beneath it, which may lead to marked exaggeration of the natural ridges and other markings. The skin and subcutaneous tissues, and other parts, such as the tongue, which are enlarged, present an increase of the interstitial connective tissue.

The pathology of acromegaly is still altogether uncertain, and although it seems probable that the relation of this disease with affections of the pituitary may be of the same nature as the relation of Addison's disease with the suprarenal glands or of exophthalmic goitre and myxœdema with the thyroid gland, evidence is still wanting in confirmation of this view. Future investigations may show that acromegaly results from a definite alteration in some internal secretion of the pituitary gland. Enlargements of the gland, how-

ever, histologically similar to those found in acromegaly, have been met with unassociated with any symptoms of the disease.

Treatment.—The results of the treatment of acromegaly with extracts prepared from the pituitary gland have hitherto been uniformly disappointing. Of the symptoms which call for relief the most urgent is the severe headache which is so common. For this purpose antipyrin or phenacetin may be found useful.

RAYMOND JOHNSON.

HYPERTROPHIC PULMONARY OSTEO-ARTHROPATHY

This name was first proposed by Pierre Marie in 1890 for certain changes in the bones and joints which are occasionally found in association with chronic diseases of the thoracic viscera, but it is scarcely doubtful that at least two, and probably more, distinct conditions have been described under the name. One condition is allied to, or identical with, the osteo-arthritis of septic origin met with in connection with urethral and other discharges; the other is characterised by extensive periosteal changes in the long bones, and sometimes by ulceration of cartilage and effusion into the joints. Both conditions are accompanied by changes in the ends of the fingers and toes, very similar to those seen in ordinary "clubbing," and all the cases have been brought together on account of their association with some form of intrathoracic disease. When, however, it is pointed out that this may be pleurisy, empyema, bronchiectasis, pulmonary tuberculosis or new growth, or some form of heart disease, it is obvious that the bond of connection may be less a natural than an artificial one. Nor is there any support for the theory that the condition is of an inflammatory nature determined by toxins, which have been found in connection with disease of the thoracic viscera. One of the original cases described by Marie has since been proved by post-mortem examination to be one of acromegaly. Many of the cases characterised by periosteal changes have been accompanied by pulmonary tuberculosis and by tuberculous lesions elsewhere, thus supporting Mr. Thorburn's theory that these cases at all events are examples of a widely-spread chronic tuberculosis. It should also be added that the possibility

of some of the recorded cases being syphilitic does not appear to have been fully considered. It remains, therefore, a matter of doubt as to what proportion, if any, of the cases of pulmonary osteo-arthropathy constitute a distinct type analogous to acromegaly or osteitis deformans. Adult males appear to be most liable to become affected, although children have been known to develop the disease.

Symptoms.—From what has been said it would appear impossible to describe a typical case. In some instances, however, there is marked enlargement of the hands and feet, and the adjacent parts of the forearms and legs. In the hands the enlargement is most noticeable in the fingers, more particularly in the terminal phalanges, which become bulbous. The nails also are much enlarged and unduly curved, overlapping the ends of the fingers, and present a marked longitudinal striation, with a tendency to split in the same direction. In contrast with the enlarged fingers the rest of the hand shows but little enlargement, but in the region of the wrist the swelling is again very marked, and is due chiefly to thickening of the lower parts of the radius and ulna. In the lower limbs the condition is in every respect similar but usually less noticeable, although in Marie's first case the lower part of the leg and the malleolar region were much enlarged. The knees and elbows may also be found distinctly swollen as the result of effusion into the joints, and a variable degree of limitation of movement may result. Another symptom which has been observed in pulmonary osteo-arthropathy is kyphosis in the dorso-lumbar region of the spine, sometimes in association with scoliosis; this may, however, according to Marie, be a late development. As a result of this spinal curvature the chest may also be more or less deformed. The face shows no change except, perhaps, a bulbous enlargement of the nose, and the cranial bones are unaffected.

The recognition of osteo-arthropathies of the kind under consideration is dependent upon their association with intrathoracic disease. In the cases particularly described by Marie some similarity may be observed with acromegaly, the most obvious differences being that the face is not affected, and that the enlargement of the hands and feet affects chiefly the terminal phalanges.

Prognosis.—In those cases which appear to be of the nature of a septic osteo-arthritis, the changes may subside entirely if the thoracic affection, such as a chronic empyema, is cured. In the tuberculous cases the course is usually progressive.

Morbid anatomy.—In only a few instances have the affected

bones and joints been examined after death. In a case carefully studied by Messrs. Thorburn and Westmacott (*Tr. Path. Soc. of London*, 19th May 1896), the osseous lesions were essentially those of a periostitis with some sclerosis, while the joint changes consisted in a remarkable series of symmetrical erosions of the articular cartilages with occasional evidences of synovitis.

The **treatment** is that of the intrathoracic disease with which the bone and joint changes are associated. Any suppurating cavity should, if possible, be freely drained.

RAYMOND JOHNSON.

OSTEOMALACIA—MOLLITIES OSSIUM

This disease is characterised by a more or less widely-spread softening of the bony skeleton, which results more particularly in the occurrence of spontaneous fractures and in a yielding of the softened bones in the direction of greatest pressure, sometimes to such a degree as to occasion the most extraordinary deformities. Osteomalacia occurs almost exclusively in adult life, most frequently in the third decade, and is far more common in women than in men. The symptoms are frequently first noticed during the puerperal state, and with each succeeding pregnancy a rapid advance in the symptoms may occur. In this country the disease is exceedingly rare, but in some parts of Europe, especially Italy, Switzerland, and South Germany, it is more common. Nothing more is known with regard to its causation than that the disease seems to be favoured by insufficient food, exposure to cold and wet, and unfavourable hygienic surroundings. An apparently similar affection is occasionally met with in the lower animals.

Symptoms.—Before the changes in the bones are sufficiently advanced to cause recognisable deformities, there is usually a period in which the chief symptoms are pains in the trunk and limbs, especially about the pelvis and the lower part of the back, muscular weakness, difficulty in walking, and loss of flesh. The occurrence of spontaneous fracture is sometimes an early symptom. The fractures are often multiple, and may occur in the long bones or in the ribs. The most noticeable deformities resulting from the bony

softening are those of the pelvis, spinal column, and chest. The deformity of the pelvis may be of a degree not met with in any other disease, and may offer an insuperable obstacle to natural delivery. In accordance with the lines along which the weight of the trunk is transmitted from the sacrum to the heads of the thigh-bones, the acetabula and the promontory of the sacrum are pressed together, with the result that the symphysis pubis is pushed forwards in the form of a prominent beak, whilst the pubic rami are closely approximated, and the iliac bones are often sharply folded upon themselves. The oblique diameters of the pelvis are greatly diminished. The spine develops curvatures, chiefly in a lateral direction, and the chest becomes deformed as the result of the falling in of the sides of the cavity. In severe cases the bones of the limbs may exhibit considerable deformities, and even the skull may be altered in shape as the result of pressure upon it. Amongst the alterations which have been found in the urine the most common is an excessive amount of phosphates.

The **diagnosis** of osteomalacia in the earliest stages may be impossible, whilst, when the phenomena of the disease are established, there is no other affection with which it can well be confounded. The pains which so frequently occur early are likely to be regarded as "rheumatic," or due to caries of the spine, whilst in some instances the weakness of the lower limbs, especially as it may be associated with increased knee-jerk and ankle-clonus, has been regarded as an early symptom of some affection of the spinal cord. At that period of the disease when spontaneous fractures especially occur, care must be taken not to confound osteomalacia with *fragilitas ossium*. In this affection, which may be inherited, the only phenomenon is the tendency to the occurrence of fracture from altogether trivial causes; the fractures usually unite readily, there is no interference with the general health, and no softening of the bones followed by deformity. It must also be remembered that in some cases of carcinoma multiple secondary deposits may occur in the bones and occasion spontaneous fractures, and that if the primary growth is in an inaccessible position, the nature of the case may be obscure.

The **course** of mollities ossium is usually progressive, and, as already noticed, may be hastened by the occurrence of pregnancy. Death usually results in a few years from general weakness, but is not uncommonly hastened by some intercurrent affection of the lungs. In some instances the disease appears to become arrested in its earlier stages.

Morbid anatomy and pathology.—Even in a case of

ordinary severity, the softening of the affected bones is such that they may easily be cut with a knife, and it has been known to advance to such a degree that a rib or even a long bone could be tied into a knot. The Haversian canals of the compact tissue, the cancellous spaces and the medullary canal are all enlarged and contain a reddish semi-fluid material. Cystic spaces, sometimes of considerable size, are occasionally present in the interior of the bones. The osseous trabeculae undergo a process of decalcification, which begins in their peripheral layers. This absorption of formed bone offers a marked contrast to the failure in deposition which characterises rickets.

Many ingenious theories have been advanced in explanation of the bone changes, but whether the true excuse lies in some dietetic error or whether the disease is infective in nature or dependent upon some trophoneurosis is not known.

Treatment.—Although the administration of phosphorus has appeared in some cases to be beneficial, the medicinal treatment of osteomalacia can only be regarded as unsatisfactory. Every attention must be given to the food and general surroundings of the patient. In view of the intimate relation which undoubtedly exists between the disease and the puerperal state, removal of the ovaries has recently been practised with a degree of success in checking the disease which would appear fully to justify a further trial of this method of treatment. The deformity of the pelvis may be such as to render delivery *per vias naturales* impossible, and to necessitate Cæsarean section.

RAYMOND JOHNSON.

GIGANTISM

Giant growth must not be confounded with diseases in which the bones or soft parts undergo hypertrophic changes. The abnormal size of the body may be noticeable at birth, but more frequently growth only becomes exaggerated during the early years of life. The natural proportions of the body are more or less accurately maintained, but often the length of the lower limbs is excessive. Gigantism is usually associated with debility, and death occurs early. Giant growth occasionally involves only a part of the body, as, for

instance, one limb, or even one or more of the fingers or toes (macroductyly). In such cases the enlargement is usually congenital.

RAYMOND JOHNSON.

LEONTIASIS OSSEA

This very rare disease, the true nature of which is unknown, was first described by Virchow. It is characterised by the formation of masses of osseous tissue in connection with certain bones of the face or cranium, and begins usually in early life. When it attacks the bones of the face, particularly the upper jaws, it may gradually cause very hideous deformity; the bony outgrowths may block the nasal fossæ and encroach upon the orbits, displacing the eyeballs and sometimes causing blindness. From the face bones the hyperostosis may slowly spread to those of the cranium, or the disease may begin in the latter, especially in the frontal bone. Severe pain may be caused by pressure on the branches of the fifth nerve.

Diagnosis.—In its earliest stages leontiasis ossea is likely to be confused with syphilitic osteitis, but the steady increase of the bony enlargement, in spite of the administration of iodide of potassium, will sooner or later exclude that disease. From a simple osseous tumour it is distinguished by the enlargement of the affected bone itself, which accompanies the formation of the irregular outgrowths, and usually by the fact that more bones than one are affected. In its very slow course leontiasis differs from an osteo-sarcoma. From acromegaly it is at once distinguished by the absence of any changes except in the bones of the cranium and face, and by the fact that in the latter the enlargement is not uniform.

Morbid anatomy.—The diseased bone is unusually vascular and consists of coarsely cancellated tissue. In the case of the skull bones, all distinction between the diploe and the inner and outer tables may be lost. Examined microscopically, the normal medulla of the spaces has been found to be replaced by a delicate connective tissue.

Treatment.—In a few instances relief has followed the complete removal, by operation, of the affected bone. In advanced cases little can be done beyond perhaps the removal of any bony outgrowth which is causing distress.

RAYMOND JOHNSON.

OSTEITIS DEFORMANS

This remarkable affection, which is characterised by enlargement and alteration in shape of certain parts of the skeleton, was first definitely described by Sir James Paget in 1876, and although since that time a very considerable number of cases have been recorded, nothing of importance has been added to our knowledge of the disease.

Osteitis deformans is a disease of the middle period of life and rarely occasions any marked symptoms before fifty. It occurs in both sexes, but with slightly greater frequency in males, and usually manifests itself in individuals whose previous health and family history are free from any points of etiological importance.

Symptoms.—Frequently, but not invariably, the alterations in the bones are preceded by vague pains in the limbs. The part in which the enlargement is first noticed is not always the same, but most often it is either the cranium or one tibia. The progressive increase in the size of the head is often one of the most striking features of the disease, so that, as in Paget's first case, the patient requires year by year a hat of larger size. The preponderance of the cranial over the facial enlargement—the reverse to what obtains in acromegaly—renders the upper part of the head larger than the lower, in contrast to the opposite condition presented by the latter disease. If the changes begin in a long bone, such as the tibia, it is the enlargement of the shaft of the bone which attracts attention, and is accompanied by the gradual production of an exaggerated curvature. The changes tend sooner or later to assume a symmetrical distribution.

In the more advanced stages of the disease the patient's general appearance is very striking, and in the erect position has aptly been described as "ape-like." The upper part of the spine is very strongly arched, so that the head and shoulders are thrown prominently forwards, and when the upper limbs are hanging the fingers may reach nearly to the level of the knees. The patient's height may thus be diminished to the extent of many inches, although the length of the long bones may be actually increased. The cranium is greatly and uniformly enlarged, whilst the bones of the face, excepting perhaps the lower jaw and malar bones, escape, so that by contrast the face appears small.

The enlargement and deformity of the long bones of the upper

limbs are rarely so marked as in those of the lower, but the clavicles especially may be thickened and unduly curved.

In the lower limbs the changes are usually very striking. The femora become strongly bowed outwards and the tibiæ forwards, so that when the feet are placed together the knees are widely separated. The shafts of the thigh- and leg-bones present usually great enlargement, which in the case of the tibia effaces the natural surfaces and borders and converts the bone into an irregularly rounded massive column. The great trochanter is rendered unduly prominent, not only by the enlargement of the bone, but by a diminution in the angle between the neck of the femur and the shaft. The patellæ also partake in the enlargement.

Even in the later stages of the disease the patient's health seems only to suffer from want of exercise, and the mental power remains unimpaired. In more than one recorded case of osteitis deformans blindness has slowly supervened, as the result of choroiditis or retinal hæmorrhages.

Diagnosis.—In the earliest stages, if the enlargement be limited to one bone, such as the tibia, the changes may readily be confused with those of a chronic syphilitic inflammation, until the steady invasion of other bones and the bending which accompanies the enlargement indicate the true nature of the case. The chief points of difference between osteitis deformans and acromegaly are indicated in the description of the latter disease.

Prognosis.—The course of osteitis deformans is progressive but exceedingly slow. It only appears to shorten life by rendering the patient unable to combat any intercurrent affection which may arise, particularly chest complications, and from these death is especially liable to occur, as a result of the rigid condition of the chest wall. In such a considerable proportion of the recorded cases death has been preceded by the development of malignant disease that the association can hardly be regarded as accidental. The tumours are sarcomatous in nature and often multiple, and in some instances the tumour formation has in the first instance been recognised in one of the enlarged bones.

Morbid anatomy.—The changes occurring in the bones in osteitis deformans appear to be of a chronic inflammatory nature. The compact tissue is greatly increased in thickness and converted into a dense cancellous substance, which is indistinguishable from the condensed cancellous bone of the articular extremities. The periosteum is normal, but the medullary cavity is more or less encroached upon. The microscopic changes are chiefly those of

rarefying osteitis; the Haversian canals are enlarged, and contain a cellular tissue around the vessels. The thickened cranial bones consist of dense porous osseous tissue, in which all distinction between the tables and the diploe may be lost.

Nothing is known of the true pathology of osteitis deformans nor of the relation existing between the disease and the development of sarcomatous growths, with which, as already pointed out, it is liable to be complicated.

No **treatment** has hitherto proved of any avail. Iodide of potassium has been given with negative results.

RAYMOND JOHNSON.

*THE BLOOD UNDER NORMAL CONDITIONS, AND THE
METHODS OF EXAMINING IT CLINICALLY*

This subject will be considered under the following heads:—

I. Development of the blood; II. General characteristics; III. Reaction; IV. Specific gravity; V. Chemical composition; VI. Hæmoglobin; VII. The effect of respiration; VIII. The coagulation of blood; IX. Microscopy: morphology of blood, (*a*) The red corpuscles, (*b*) The white corpuscles, (*c*) The platelets, (*d*) The plasma granules; X. Note on the preparation and examination of blood films, etc.

I. DEVELOPMENT OF THE BLOOD

In amniotes the blood arises from specific cells (angioblasts) of the mesoderm; the part where it arises is known as the blood germ and is outside the body of the embryo. Reticulate thickenings surrounding lacunæ of irregular shape appear in the mesoderm. This network very soon shows patches of a reddish-yellow colour containing hæmoglobin. These are known as blood islands. The strands of the network before long acquire a lumen; the blood islands are found on the inner surface of these new vessels, and the cells of which they consist become free nucleated red blood cells. By extension and growth the vessels, which of course consist only of endothelium, are soon found to be within the embryonic area. New vessels, however, arise independently by transformation of mesenchymal cells within the embryonic area, and join up with those growing in from without. The first formed red blood cells then are nucleated spherical bodies containing hæmoglobin, capable of amœboid movement and multiplying by karyokinesis. Two kinds have been observed, viz. megaloblasts and normoblasts, the former being of larger size and having a large paler staining nucleus. These megaloblasts have been by some regarded as older and degenerate forms of normoblasts, but it is probable that the two have not a common origin, inasmuch as the larger cell is under normal circumstances found exclusively in intra-uterine existence.

These early red cells increase rapidly in numbers, but disappear at latest soon after birth. How they disappear is unknown; one view, however, is that the nucleus is extruded and the cells become red corpuscles. After birth new vessels are still formed in the same way as before, but no red cells are produced within them. The supply is probably kept up by the bone marrow, and possibly by the spleen, where nucleated amœboid cells whose protoplasm contains hæmoglobin are to

be found. Presumably these cells are transformed into red corpuscles by atrophy and extrusion of the nucleus, the cell body itself becoming biconcave. In the human embryo at one month nucleated red cells only are found, at two months red corpuscles have appeared, and at three months these latter form the majority of the cells present. The duration of life for individual red corpuscles has been estimated at from three weeks to one month. Under normal conditions their destruction is carried on to some extent by the spleen, where the earlier stages of disintegration can always be observed. The final resolution, with liberation of hæmoglobin, perhaps takes place in the liver, inasmuch as bilirubin is certainly derived from hæmoglobin, and neither of these pigments is to be found free in the splenic vein.

The white cells do not appear so early as the red, and those that first appear are probably wandering mesenchymal cells. Later the supply is provided partly by the lymphoid tissues of the body, where a process of karyokinesis may at all times be observed, and partly by division of white cells in the blood itself. Where each variety of white cell arises has not yet been definitely made out, but one view is that all the white cells excepting coarsely granular oxyphils (eosinophils), which reproduce their like, give rise on division to the lymphocyte. Lately it has been shown that in experimental leucocytosis the fat of the bone marrow is absorbed and hyperplasia occurs, the cells which are increased being the myelocytes, thus pointing to these cells as the origin of the finely granular oxyphil leucocyte (polymorphonuclear neutrophil). The origin of the platelets is unknown, but their presence in the circulating blood shows them to be a normal constituent of that fluid.

II. GENERAL CHARACTERISTICS

Human blood is an alkaline, slightly viscid fluid having an average specific gravity of 1058, and a colour which varies from a bright scarlet to a dark purplish-red, according to the amount of oxygen which its hæmoglobin happens to contain.

The total colour effect of blood is due to several factors, viz. to the colouring matter of the red corpuscles—oxy- and reduced hæmoglobin, to the colouring matter of the serum—serum lutein, to the reflection of light from the innumerable surfaces presented by the corpuscles, to the proportion of leucocytes present, and to the amount of fat in the blood plasma at the time.

Alterations in the colour of blood occur under certain abnormal conditions—it is clearer and paler in severe anæmias, paler but less translucent in advanced leukæmia and also in the lipæmia of diabetes; it may become extremely dark in asphyxia from want of oxygen, while it assumes a more or less permanent bright vermilion in suffocation from absorption of carbonic oxide, as in poisoning by charcoal fumes, lighting

gas, fire-damp explosions, and many cases of death in burning buildings. In poisoning by cyanides a somewhat similar colour is always seen.

The total amount of blood in the body has been variously estimated, the average, as usually stated, being from one-twelfth to one-thirteenth of the body-weight. There is good reason to believe, however, that this estimate is too high, and that the total mass of the blood does not amount to more than between one-twentieth and one-twenty-first. According to this estimate a healthy adult, weighing 70 kilos., or 11 stone, has about 3.2 litres of blood, about $5\frac{1}{2}$ pints.

The volume is markedly increased both in chlorosis and in pernicious anæmia. After severe hæmorrhage the actual volume is rapidly restored. The time taken for the blood to again become normal, however, depends on the amount lost. A loss of under 1 per cent of the total blood is stated to be made up in from two to five days, while two to five weeks are required to make good a loss of 3 or 4 per cent, and the process may be much slower where the hæmorrhage, though small in amount, is persistent.

III. REACTION

Blood when freshly drawn is alkaline to litmus, and under no circumstances during life is there any very great alteration in its reaction; during diabetic coma alone has the blood been proved to be acid. The reaction in the case of the plasma is due to the presence of disodic phosphate (Na_2HPO_4) and to bicarbonate of soda (NaHCO_3).

After blood has been withdrawn from the body the alkalinity diminishes and the reaction may become acid, but under normal circumstances during life it is equal to about 0.2 grm. of sodium hydroxide for every 100 c.c. of blood. It rises after food and falls after muscular exertion. It is lowest in the morning and in the evening. These changes may be tested clinically by using a graduated series of glazed litmus papers, leaving the drop of blood in contact with the paper for ten to twenty seconds and then wiping it away with a clean piece of linen wet with normal saline solution. The method, however, is not free from objections.

IV. SPECIFIC GRAVITY

The specific gravity of the blood as a whole in healthy adults varies from about 1050 to 1066, being lower in women than in men. At birth it may be as high as 1066, but falls very rapidly, being as low as 1049 at the third year.

It varies according to the part from which the specimen is taken; where the circulation is slow, as over the shin, the specific gravity is higher than where the circulation is more rapid, as in the finger. It is lowest in chlorosis, in secondary anæmias, and after hæmorrhage, and

markedly so in pernicious anæmia, while it is high in diabetes and after severe injuries, or in any conditions where shock is marked. It may be most readily estimated by Hammerschlag's method. Chloroform and benzole are mixed together in a sufficiently tall glass vessel till their specific gravity is about that of normal blood. A drop of blood is drawn up into a fine pipette and blown out under the surface of the mixture. If the bead of blood rises, the mixture must be made lighter by the addition of more benzole; if it falls, the mixture must be made heavier by the addition of more chloroform. When the blood neither rises nor falls, the specific gravity of the mixture, which is now the same as that of the blood, may be taken, and the necessary correction for temperature made.

The specific gravity of blood has in many cases been found to vary directly as the richness in hæmoglobin, an alteration of 4.46 per mille in specific gravity representing an average alteration of 10 per cent hæmoglobin, but this does not hold good where the normal proportions between the red corpuscle count and the hæmoglobin estimation vary to any great extent.

V. CHEMICAL COMPOSITION

From blood plasma it has been found possible to obtain a considerable number of inorganic and organic bodies. The exact relationships of the members of the former class is unknown, but they include chlorides, carbonates, phosphates, and sulphates of sodium, potassium, magnesium, and calcium, the most abundant salts being sodium chloride and sodium carbonate. These salts are held in solution by the water of the plasma, which constitutes 90 per cent of its total volume.

Of the organic bodies found in plasma, the most important are the proteids. These consist of serum albumins, of fibrinogen and serum globulin, and of nucleo-proteids, a class of bodies rich in phosphorus. The probability is that the last named are derived almost entirely from the white corpuscles and the platelets.

Besides proteids certain other nitrogenous bodies, of which urea is the most important, are present in plasma. Whether or no uric acid is normally present has not been definitely made out. Kreatinin is always found.

Under this heading may also be considered the various ferments that are supposed to exist in the blood. Starches are converted into sugar by blood, both within and outside the body, but whether there is a further glycolytic action is uncertain.

The formation of fibrin from fibrinogen is the most important ferment action exhibited by the blood, but it is very doubtful if the ferment exists as such in the circulating fluid—probably only its precursor, the so-called prothrombin, is actually present.

With the exception of small amounts of fats which are increased after meals and sometimes in certain diseases, such as diabetes and chronic nephritis, the only remaining organic substance of importance is dextrose. This is present under all circumstances in the plasma. During digestion, if the diet is rich in carbohydrates, the portal vein blood contains a considerable excess of it as compared with blood drawn from other parts. The normal amount of dextrose is 0.12 per cent of the total blood, whenever it reaches 0.25 per cent it appears in the urine, and under no circumstances, even in severe diabetes, does it exceed 0.48 per cent.

The inorganic substances obtained from the red corpuscles show a very marked preponderance of potassium, and here too the phosphates are in excess of the chlorides, the opposite of what obtains in the plasma and in the white corpuscles. Their chief organic constituent is hæmoglobin, while in the white cells and probably also in the blood platelets it is nucleo-proteid.

VI. HÆMOGLOBIN,

to which the colour of the red corpuscles is due, is a highly complex substance which by the action of certain reagents can be split up into an albuminous body, the constitution of which probably varies in different animals, and hæmatin, this latter containing the iron which is characteristic of hæmoglobin.

Iron is present to the extent of 0.336 per cent in hæmoglobin crystals. Traces of the metal are found in nuclei and in nucleo-proteids; the total amount of iron in the blood of a man of average weight being from 2.5 to 3 grms. In all probability the iron required for the formation of hæmoglobin is obtained mainly in the form of organic compounds in the food, while possibly the iron which remains after hæmoglobin has undergone destructive changes in the liver may furnish a further supply for this purpose. That hæmoglobin undergoes such destructive changes in the liver is rendered probable by the fact that the number of red corpuscles in the blood as it leaves the liver is always found to be less than in that coming to the liver.

Several of the body pigments originate from hæmoglobin, notably bilirubin, which is derived from iron-free hæmatin. Urobilin, too, which is identical with stercobilin, the main pigment of the fæces, can be obtained from bilirubin by the action of bacteria normally present in the bowel. Urochrome, the main pigment of the urine, has been obtained by reduction from urobilin.

Hæmoglobin has been obtained in crystalline form from the blood of most animals, but far more readily in some than in others. The shape of the crystals varies somewhat—in man it occurs as rhombic prisms. Crystals of reduced hæmoglobin have been observed to deposit

spontaneously in blood preparations from cases of severe pernicious anæmia before treatment, in leukæmia, pyæmia, and certain other diseases. Under these circumstances they may be obtained in a drop of blood placed on a slide and covered with a cover glass as soon as evaporation is evident at the edges.

Hæmoglobin and its derivatives furnish characteristic spectra. These may be examined for clinical purposes by means of any good direct vision spectroscope, such as that of Browning or the rather larger instrument of Heele which is fixed on a small stand.

The spectrum of oxyhæmoglobin shows two absorption bands—one which is seen on the E side of the sodium line, and the other, which is broader and fainter, which lies on the D side of E. These absorption bands are visible in extremely dilute solutions of blood, even when the proportion is no more than one to eight or ten thousand in a layer of 1 cm. depth, as in the ordinary hæmatinometer, but are best seen when blood is diluted with about eighty times its volume of water.

A solution of oxyhæmoglobin which shows so much absorption that the two bands are fused and only a faint line of green is visible, has a strength of 0.8 per cent.

Oxyhæmoglobin, $\text{Hb} \begin{smallmatrix} \diagup \text{O} \\ | \\ \diagdown \text{O} \end{smallmatrix}$, can be readily deprived of its oxygen by suitable reducing agents such as ammonium sulphide in glycerine, and the spectrum then shows a single band situated between D and E.

The spectrum of the compound formed by carbon monoxide and hæmoglobin greatly resembles that of oxyhæmoglobin, and to detect the difference it is necessary to closely compare the solutions and to bring them as nearly as possible to the same strength. The two absorption bands of CO hæmoglobin are slightly nearer the violet end of the spectrum than those of oxyhæmoglobin. A great difference between the two, however, and one which can be more readily detected, is the fact that on adding reducing agents to CO hæmoglobin the spectrum remains unaltered.

The most delicate test for CO hæmoglobin is dilution with water. A solution of oxyhæmoglobin so dilute that there is neither colour nor spectrum contrasted with a similar dilution of CO hæmoglobin shows that the latter has a pink tint when viewed in the length of a column of the fluid in an ordinary test-tube.

Other derivatives of hæmoglobin which give characteristic spectra are methæmoglobin, $\text{Hb} \begin{smallmatrix} \diagup \text{O} \\ \diagdown \text{O} \end{smallmatrix}$, hæmatin, and hæmochromogen. The first

of these, which is produced during life by certain drugs such as antifebrin, phenacetin, amyl nitrite, and chlorates, and has also been found in old blood extravasations, gives a spectrum showing four bands, the most intense of which lies to the D side of the C line. This spectrum closely

resembles that of hæmatin in acid solution, but differs from it in that on the addition of ammonium sulphide the spectrum of oxyhæmoglobin is produced at first and subsequently that of reduced hæmoglobin.

The hydrochloride of hæmatin (hæmin) crystallises characteristically, and the production of these "Teichmann's crystals" forms a delicate test for blood of considerable medico-legal value. A drop of blood, or some of the suspected material rubbed out in a little water, is placed on a glass slide, and to this a crystal of salt may, but need not necessarily, be added; the mixture is then heated with a drop or two of glacial acetic acid. After it has boiled it is set aside to evaporate, and the hæmin separates out as minute dark red or almost black prisms. If a potash salt be added instead of sodium chloride, larger crystals are obtained. Rhombic crystals of an orange colour are sometimes found at the margins of old blood clots, apoplectic cysts, etc. These are known here as hæmatoidin crystals; they are in reality crystals of bilirubin.

Hæmochromogen is obtained when an alkaline solution of hæmatin is reduced by ammonium sulphide. Its spectrum, which shows a well-marked band between D and E, and another to the F side of E, is a good test for blood.

The estimation of hæmoglobin for clinical purposes is of great importance in the different forms of anæmia.

The hæmoglobinometer of Dr. Oliver based on Lovibond's tintometer is the best instrument for the purpose.¹ It consists of a pipette for measuring the blood, a cell into which the blood is discharged from the pipette and in which it is mixed in definite amount with distilled water, and a scale of standard tints split up into twelve definite gradations, and arranged in two slabs of six each, with which the specimen is compared by candle-light through a dark tube provided for the purpose.

The instrument is used as follows:—

The pipette is cleaned by passing a needle and darning cotton through it, the needle being pushed in at the point and not at the base of the pipette. Blood is drawn from the middle of one side of the terminal joint of a finger or thumb, the "stabber" or a lancet, but not a needle, being used for the purpose; whichever instrument is used it should be clean and extremely sharp, and the blood should be drawn by a rapid in-and-out stroke, and not by pressing it into the flesh. If the patient is very anæmic, friction may be used or the hand may be immersed for a few minutes in hot water, but constriction of the part is not admissible.

As soon as the bead of blood is judged to be sufficiently large, the polished point of the pipette is applied to it and the blood flows up by

¹ Dr. Haldane has quite recently brought out a modification of Gowers' Hæmoglobinometer, which has the great advantage of possessing a constant standard, viz. a solution of CO hæmoglobin. It is accurate, compact, and inexpensive, and can be used as well by daylight as by artificial light.

capillary attraction. It must entirely fill the pipette and show no break in the column of blood. All blood on the outside of the pipette is now rapidly and completely wiped away with the finger, and the rubber nozzle of the larger dropping pipette, which has been filled with distilled water, is applied over the base of the blood pipette. The blood is then washed out into the cell provided for the purpose. The cell is filled to the top, well stirred with the handle of the pipette, and the cover glass (which has a slightly bluish tint) is applied. The cell should be so full that when the cover glass is on, a small bubble of air is seen, as in a spirit-level, but no fluid has been driven out of the cell into the trough which surrounds it.

The specimen and the standardised scale are now placed under the camera-tube for comparison, illuminated equally and solely by the Christmas candle, placed in front of them. A small disc of green glass will be found on one side of the top of the viewing tube, and the eye may be rendered more sensitive to red by looking for a second at the candle flame through this. If the tint of the blood solution is considered to lie between two numbers on the scale, which represent percentages of hæmoglobin differing by tens, the specimen is placed opposite the lower number, to which tinted glass riders are added till an exact match is obtained, a slip of quite colourless glass being placed on the blood cell to counterbalance the effect of the glass itself. A separate rider is provided for each set of six gradations, inasmuch as the value of a rider is double in the lower as compared with the upper set of six gradations.

Solly's small dark chamber made to hold the light, the specimen, and the colour scale is more convenient than the camera-tube usually supplied with the instrument.

VII. THE EFFECT OF RESPIRATION

Arterial blood contains about 21 volumes of oxygen, some 40 volumes of carbonic acid, and from 1 to 2 volumes of nitrogen for every 100 volumes of blood. Venous blood, on the other hand, contains from 8 to 12 volumes of oxygen, about 46 volumes of carbonic acid, and 1 to 2 volumes of nitrogen, for every 100 volumes of blood. The nitrogen is simply held in solution, but by far the greater amount of the oxygen and of the CO_2 is chemically combined with certain substances in the blood—with hæmoglobin within the red corpuscles in the case of the oxygen, and in the case of the carbonic acid with sodium as the bicarbonate in the plasma (two-thirds), and with the hæmoglobin and other substances in the corpuscles (one-third).

The oxygen of the blood comes from the air inspired into the lungs—the carbonic acid from the tissues, as a result of their metabolism. Whether or no the normal exchange of gases between the inspired air

and the blood, and between the blood and the tissues can be entirely accounted for by the law of diffusion is still undetermined, but it is possible that the gaseous exchange is dependent on the activity of the pulmonary epithelium, since the normal oxygen tension of blood is very much higher than was till quite recently supposed.

VIII. THE COAGULATION OF BLOOD

More than a hundred years have elapsed since the discovery was made that the coagulation of blood is in reality the formation within it of a substance, fibrin, not previously present as such, yet the chemical processes involved in the phenomenon are not even now fully understood. Essentially it consists in the formation of the insoluble proteid body fibrin from the soluble proteid body fibrinogen, and this change, which involves a splitting up of the latter, is brought about by the action of a ferment, formerly known as fibrin ferment, but now designated thrombin.

Thrombin, however, although it can be obtained by extraction with water or saline solution from blood clot, and also from various organs, does not exist as such in the circulating blood, and the formation of it, and consequently coagulation, is delayed by anything which tends to keep the blood in a living condition.

Certain body fluids such as hydrocele, and pericardial fluids which do not coagulate spontaneously, contain fibrinogen in solution and therefore clot on the addition of thrombin. Many researches have been made in order to throw light on the processes involved in the production of thrombin. Thus it has been proved that the watery extract of blood clot or of blood precipitated by alcohol contains calcium sulphate, and that if this be completely removed the clot-producing property is lost, but that it is again restored by adding either the same or another salt of calcium, or of barium or strontium. The importance of such a salt has been further proved by mixing blood drawn directly from the living vessels with soluble oxalates, soap, or fluorides, in small but sufficient quantity. Such blood may not coagulate, as most of its lime salts are precipitated in this way. On now adding some soluble lime salt coagulation ensues. The watery extract of alcohol-precipitated blood contains, besides the sulphate of lime just mentioned, a proteid substance rich in phosphorus, *i.e.* a substance belonging to the class of bodies known as nucleo-proteids.

It is probably derived from the leucocytes either as a result of their destruction or as a secretion from them, and it corresponds with the bodies obtained by extraction of the various glandular organs with saline solutions, and called originally by Wooldridge tissue-fibrinogens. These bodies when injected in sufficient quantity into the circulation produce intra-vascular coagulation, and the same thing may be brought about by

the injection of snake venom and certain other substances. Injected slowly and in smaller amounts they not only do not induce intra-vascular clotting but produce a state of non-coagulability of shed blood.

This latter state of non-coagulability of shed blood is also produced by injection of other bodies such as albumoses, and leech extract, and coagulation of such blood can be brought about by adding lime salts or nucleo-proteids to it. Further, if such blood be kept at 0° C. for some time, a precipitate forms in it which consists of nucleo-proteid, and in the presence of soluble lime salts has the properties of thrombin. The nucleo-proteid itself is known therefore as prothrombin.

Blood rendered non-coagulable by injection of albumoses is less alkaline, and contains far less CO_2 than is normally present, and to this is due, in some way, its peculiar characteristic, inasmuch as the passage through it of a stream of CO_2 causes it to coagulate. The precise chemical explanation of the phenomenon is however still lacking.

It thus appears that the coagulation of blood is due to the splitting up of fibrinogen and consequent formation of fibrin by the agency of a ferment, thrombin, which is not present as such till blood is shed, or till the vessel wall is injured, and that this ferment is produced by the interaction of a nucleo-proteid, prothrombin, with the soluble lime salts of the blood, and that the nucleo-proteid is derived either from the leucocytes or the platelets, or both.

Under healthy conditions shed blood begins to clot in about 3 minutes, and the clot is completely formed in about 8 minutes. Coagulation is hindered by cold, by keeping the blood in contact with the uninjured vessel wall, or by receiving it into oil, or an oiled vessel. Opposite conditions hasten coagulation, injury to the walls of the blood-vessels probably acting on the leucocytes in the same way as contact with a rough surface or foreign body, causing them to set free nucleo-proteid.

A diminution of the lime salts or of the nucleo-proteid in the blood causes a condition of reduced coagulability.

For clinical purposes no thoroughly satisfactory method of timing the process as it occurs in small drops of blood has been devised. The most reliable instrument for the purpose is the coagulometer of Brodie and Russell.

The buffy coat of shed blood seen in various inflammatory conditions, and normally in blood drawn from the horse, is due to the subsidence of the red corpuscles before coagulation takes place. This effect is due not to slowness of coagulation nor to relative heaviness of the red corpuscles of the horse, but more probably to the presence of some substance, which in inflammatory conditions, and also in normal horse serum, increases the agglutination of the red corpuscles and so causes their more rapid subsidence.

IX. MICROSCOPY: MORPHOLOGY OF BLOOD

The solid elements of the blood are the chromocytes, called also erythrocytes or red corpuscles, the leucocytes or white corpuscles, the blood platelets, and the plasma granules.

(a) **The red corpuscles** are biconcave, non-nucleated discs, with a diameter averaging 7μ . They are of fairly uniform size and shape, but in certain diseases, notably pernicious anæmia, some of the corpuscles are much larger (megalocytes) and some much smaller than normal (microcytes), while the shape is frequently distorted in a greater or less degree, this condition being known as poikilocytosis.

In specimens of blood stained with a mixture of dyes they show under normal conditions an affinity for the acid dye, but in certain diseases some of the elements may take up more or less of the basic dye as well. This condition is known as polychromatophilic change.

Under some circumstances red corpuscles may be found containing a number of granules which stain intensely with basic dyes such as methylene blue. These granules vary greatly in number and size, when numerous being often so small as to be difficult to make out even with very high magnification, and when few in number being large and resembling a group of cocci, diplococci, and short rods. They are most readily to be found in pernicious anæmia and leukæmia, and in the anæmia of lead poisoning. The condition is known as granular degeneration and may affect any variety of red cell whether nucleated or not.

Two kinds of nucleated red cells are found in blood, but, except *in utero* or immediately after birth, only under pathological conditions. These are known as megaloblasts and normoblasts.¹ The latter are the more commonly seen, and are about the size of an ordinary corpuscle, sometimes larger, but possess one, sometimes two or more, round nuclei, which stain intensely. Megaloblasts, which, when present in comparatively large numbers, have been considered almost pathognomonic of pernicious anæmia, are of large size and have a large paler staining or granular nucleus. Both these kinds of cells are distinguished from any variety of leucocytes by the fact that the cell body contains no granules and in stained specimens is generally of the same colour as the other red corpuscles, unless it shows granular degeneration or a considerable polychromatophilic change. Although in typical examples these two varieties are readily distinguished from one another, yet in very severe anæmias atypical forms are frequent, and in the case of any particular cell it may be impossible to say under which head it should be classed.

¹ Nucleated red cells resembling normoblasts, but of small size and having proportionately less protoplasm surrounding the nucleus, are frequently classified separately as microblasts.

The nucleus of the normoblast is either eventually extruded or the protoplasm around it degenerates and leaves it free, while that of the megaloblast is said to undergo karyolysis.

To count the red corpuscles pipettes accurately graduated, a specially ruled glass slide known as the counter, and a preserving fluid for diluting the blood are employed.

As there are serious objections to various parts of the apparatus as supplied by different makers, it is best to use a set made up as follows, viz.—

The Thoma-Zeiss counter, the Zeiss cover glasses, the small Gowers' pipette 5 mm.³, the large Gowers' pipette 995 mm.³, two or three small cylindrical weighing bottles with ground-in stoppers about 2.5 cm. in height.

Various diluting fluids such as Sherrington's, Hayem's, Toisson's, are recommended; they are designed to preserve the red and to tint the white corpuscles.

One which answers very well consists of—

1.5 per cent formalin in distilled water 100 c.c., NaCl 0.5 gm., Na₂SO₄ 2.5 gm., methyl violet 10 mgrm. Some of the diluting fluid is freshly filtered, and by means of the larger Gowers' pipette 995 mm.³ of it are transferred to one of the small weighing bottles.

The patient's finger is cleaned and pricked in the way previously described. The blood should flow freely and pressure must not be applied. The first drop is rejected, and from the second exactly 5 mm.³ are drawn up into the small Gowers' pipette, and at once blown out into the diluting fluid in the weighing bottle. It is best to draw up more than 5 mm.³ and then to remove the excess with blotting paper. A little of the mixture is now drawn in and out to ensure the complete emptying of the pipette. The mixture is thoroughly stirred, and, unless a count is to be made at once, the stopper should be immediately replaced. Directly this has been done the small Gowers' pipette must be washed out with distilled water; later absolute alcohol can be used to remove the water, and the alcohol in its turn may be removed by ether. When the latter has evaporated, the pipette should be quite clean and dry and fit for use in another observation.

The Thoma-Zeiss counter consists of a glass slide in the middle of which is cemented a small glass disc ruled with squares of definite size; surrounding this disc is a piece of slightly thicker glass on which the cover glass rests. A space is thus left between the under surface of the cover glass and the upper surface of the disc and the distance between the two is known. Each small square upon the disc represents, when the cover glass is on, a cell whose capacity is $\frac{1}{4000}$ mm.³ To make a count the ruled disc, the glass around it, and the cover glass are thoroughly cleaned, the mixture in the weighing bottle is well stirred, and a very small drop of it is placed on the centre of the disc. The

cover glass is placed upon it and firmly pressed down. On holding up the slide and looking along the surface of the cover glass Newton's rings should be seen surrounding the disc. If this is not so, the cover glass is not in accurate contact, either because it is dirty or because it has not been sufficiently pressed down. The drop of diluted blood on the disc need not be large enough to cover it and must not be so large as to extend beyond it.

Now the blood has been diluted 200 times, and the capacity of each small square is $\frac{1}{4000}$ mm.³ Therefore the contents of any one such square multiplied by 800,000 will give the number of red corpuscles in 1 mm³. of blood. The white corpuscles are readily distinguished by their violet-tinted nuclei. To ensure any degree of real accuracy, it is necessary to count at least 200 squares in each of two drops of the diluted blood and to take the average; any sample drop of the diluted blood in which the corpuscles are not evenly distributed over the ruled squares must be rejected.

With the new Zeiss cover glasses a high-power objective may be used, with the old form a low-power objective with a high ocular works best. A mechanical stage, though not essential, saves much time and trouble.

The normal number of red corpuscles per mm.³ is in males about 5,000,000, and in females rather less.

(b) **The white corpuscles or leucocytes.**—A great many kinds of leucocytes have been described, and the names which have been applied to them are somewhat confusing. The commonest white cell found in blood has a deeply staining nucleus which is generally seen twisted into some fantastic shape or arranged as apparently three or four separate nuclei, though under ordinary circumstances these are nearly always connected by thin strands with one another. The body of the cell contains fine granules, which show an affinity for acid dyes (neutral dyes, Ehrlich). This is the cell the numbers of which are increased in pathological leucocytosis, and which forms the great majority of pus cells. It is known variously as the polymorphonuclear or *polynuclear leucocyte*, the polymorphonuclear neutrophil, the *finely granular oxyphil*, or the leucocyte with multipartite nucleus. Normally this form numbers 70 per cent of the leucocytes present in blood of the adult. It is amoeboid.

Much rarer than the above is a cell whose nucleus may also show evidence of its amoeboid activity, being lobed or looped, but whose body granules are much larger, and have a far greater affinity for eosin and other acid dyes. It is known as the *eosinophil*, or the *coarsely granular oxyphil*. It numbers from 2 per cent to 4 per cent of the leucocytes present in blood. Eosinophilia, which term includes both relative and actual increase of the eosinophils present in the blood, has been noted as a postfebrile condition, in certain acute and chronic

skin diseases, during the presence of worms in the intestine, and in cases of asthma, etc.

Other forms of leucocytes occur in considerable numbers in blood; these have no granules in their cell bodies, and are therefore sometimes called *hyaline cells*. They are not very readily classified, inasmuch as individual members of the group show great variations. The commonest kind of hyaline cell is one in which the nucleus is round and dark-staining, and the protoplasm surrounding it so scanty in amount and showing also such an affinity for the basic dye that the line of demarcation between the two is difficult to make out. This cell, which is known as the lymphocyte, is usually of small size, but very large forms occur, especially so in lymphatic leukæmia; in these nucleoli can frequently be seen. Variations from this kind of cell are quite common. In many cases the nucleus is paler, and may be notched or looped, and at the same time the proportion of cell body surrounding it may be much increased, while its affinity for the basic dye is decreased. The cell body, too, may acquire a sub-granular appearance, or even show one or two fine granules, having in some cases an affinity for basic, and in others for acid dyes (transitional cells).

In quite a few instances the nucleus, while staining far less deeply, is not altered in shape, and the cell body, though greatly increased in proportion, becomes much paler and perfectly clear and free from granularity. This cell is sometimes classified by itself under the name of *large mononuclear leucocyte*, and transitional cells between this and the fine granulated oxyphil (polymorphonuclear neutrophil) are described.

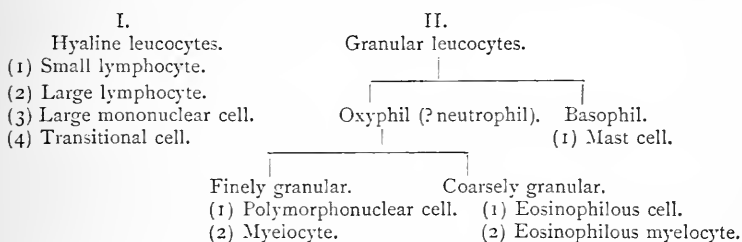
They are said together to number 2 per cent to 4 per cent of all the leucocytes in normal blood, while the lymphocytes of all kinds number 22 per cent to 24 per cent.

The fifth kind of white cell occurs in normal blood, but is rarely met with, and in health never to the extent of more than 0.5 per cent of all the leucocytes in the peripheral circulation. It is known as the *mast cell*, and has a very characteristic appearance when stained with basic dyes, such as methylene blue, its nucleus being pale and round, notched, or looped, and the cell body containing granules which are quite irregular in size, number, and distribution, and which take on, when stained with methylene blue, a dark violet colour in which either the red or the blue tint may predominate. The cell is, therefore, a basophil. Its numbers may be considerably increased in splenic myelogenous leukæmia. Very rarely a leucocyte may be found containing both oxyphil and basophil granules.

In certain diseases a new kind of leucocyte is found in the blood. This is known as the *myelocyte*, inasmuch as it has the same appearance as one kind of cell normally present in the marrow. It averages a larger size than other white cells, but quite small forms also are always to be found. It has a single large, round, pale-staining nucleus which

in most cases appears to be eccentric, and the cell body is filled with granules, generally of small size, which stain with acid dyes (neutral dyes, Ehrlich). It is not amœboid. It is met with in greatest number in splenic myelogenous leukæmia, but has also been found in the pseudo-leukæmic anæmia of infants, at the time of the crisis in pneumonia, and in severe cases of diphtheria in children, where its occurrence in considerable number is of unfavourable import. A variety of this cell is sometimes found in which the granules are much larger and stain more brilliantly with acid dyes. It is called the eosinophilous myelocyte.

The various white cells seen in blood may be tabulated as follows :—



The white cells vary very considerably in size, but are for the most part larger than red corpuscles. Some of the lymphocytes may have a diameter of no more than 5μ , while myelocytes are not infrequently seen which measure as much as 20μ .

Leucocytosis, or increase in the number of leucocytes in circulation, occurs under both normal and abnormal conditions. The former or physiological leucocytosis is found as a result of the ingestion of food, beginning one or two hours after a meal, and lasting sometimes for five or six hours. In this case the number of all the normal varieties of leucocytes except eosinophils is increased, though the lymphocytes are generally increased to the greatest extent (lymphocytosis). Physiological leucocytosis also occurs after violent exercise, short cold baths, and during the later months of pregnancy.

In pathological leucocytosis the increase of white cells is usually due to an excessive number of the polymorphonuclear cells, and its occurrence or its absence is frequently of great diagnostic value. It occurs after severe hæmorrhage, as a result of the absorption of various organic and inorganic poisons, and accompanying most inflammatory processes ; under these circumstances the most marked effect is produced by a severe infection accompanied by a strong reaction. It is, however, to be noted that in typhoid fever, tuberculosis, influenza, and measles the leucocytes are not infrequently diminished in number. In pernicious anæmia a very marked diminution may occur. *Leucopenia*, as this condition is called, may be found physiologically as a result of starvation, exposure to cold, or after prolonged cold baths.

Relative lymphocytosis, where the total white cell count is scarcely or not at all above the normal, but where the proportion of lymphocytes to other leucocytes is greatly increased, may be found in pernicious anæmia, chlorosis, and some other conditions.

The enumeration of the white corpuscles is, on account of their lesser number, more difficult to do accurately. In cases of very marked leucocytosis, as in leukæmia, the count of the white can be made at the same time as the count of the red corpuscles, but where the number of leucocytes is not much above the normal, either the blood must not be diluted more than twenty times or the counting must be repeated several times. The latter is the better way, and an advantage may be gained by inserting one of Ehrlich's stops into the eye-piece of the microscope; this gives a square aperture, and by adjusting the draw tube of the microscope till the field accurately corresponds in area with sixteen of the small ruled squares on the Thoma-Zeiss counter, a field of known area is obtained. (Messrs. Leitz make an eye-piece with an adjustable square diaphragm, very convenient for this purpose.) When this has been done, the white corpuscles present in whole fields may be counted, the ruled squares on the counter being neglected altogether. When a sufficient number of specimens has been counted in this way (fifty fields in each of ten drops of the diluted blood), the average contents of a single field is taken, divided by 16, and then multiplied by 800,000, as in the case of counting red corpuscles.

In health the number per mm.³ of blood varies, but should not be more than 10,000 even after meals, nor less than 5000 when the count is made before the morning meal. Owing to these variations blood counts and examinations should always be made at the same hour of the day.

A differential count of the varieties of leucocytes present is most readily made from ordinary stained films—the different kinds of white cells present being counted in a certain number of films. When a classification of 500 cells has been made, the percentage may be worked out.

(c) **The platelets** are small, more or less disc-shaped bodies, about a sixth of the size of a red corpuscle. They can be seen in fresh preparations; in films stained with methylene blue they usually take on a mauve or French gray tint, and are sometimes scattered over the field, but more often gathered into clumps of eight or ten. Great variations seem to occur in their numbers even in health. From 150,000 to 500,000 are present in 1 mm.³ of blood. Their numbers are most readily estimated by mixing a drop of fresh blood with a diluting and staining fluid, and in a certain number of fields of the microscope counting the proportion of platelets to red corpuscles present. If then an ordinary count of red corpuscles is made, the number of platelets in 1 mm.³ is obtained. The patient's finger, washed with soap

and water, rinsed in clean water, and finally cleaned with ether, is pricked in the ordinary way. The first drop of blood is rejected, and the second, which should flow quite freely and without any pressure being applied, is lightly touched with a drop of the staining fluid, hanging from the centre of a slide. The two are now mixed, and from the mixture a sample is taken by touching it with a clean cover glass. The latter is now placed, without allowing it to dry, specimen side downwards, on another clean slide. The platelets should be found deeply stained with the violet, quite separate from one another, freely movable, and evenly distributed in the diluting field.

The staining and diluting fluid recommended has the following composition :—

Glycerine 25 c.c., absolute alcohol 12.5 c.c., ammonium oxalate 1.0 grm., sodium chloride 1.5 grm., distilled water 62.5 c.c., dahlia (Grübler) "to saturation."

(d) **The plasma granules** are readily recognised in fresh preparations by their lively Brownian movement; at first sight they may be mistaken for cocci, as they are of very minute size. But little is known about them. They vary in numbers, are increased in certain morbid states, and diminished in starvation and cachectic conditions. Possibly they originate from the granular leucocytes.

X. NOTE ON THE PREPARATION AND EXAMINATION OF BLOOD FILMS, ETC.

All examinations of blood which have for their object the determination of the number or varieties of red or white cells or of blood platelets should be made at the same hour, and this should be at the longest time possible after a meal. This is essential if comparative results are to be obtained. For special objects special times of examination are necessary. Thus in malaria the parasites are most readily found as the temperature is going up, just before and during a rigor. The *filaria nocturna* is found, as its name indicates, at night-time, the greatest number of embryos being found in the peripheral blood at about 9 P.M.

The influence of food in producing a leucocytosis is best studied about one to two hours after a meal rich in proteids. Sometimes the increase of white cells is much delayed.

In making a general investigation of the blood the examination of a fresh drop should never be omitted. By this means poikilocytosis, the formation of rouleaux, and the presence of hæmatozoa can be most readily observed. Poikilocytosis can in fact only be said to be present when observed in such a fresh specimen, as in the case of severe anæmias the red corpuscles seem often unable to recover their natural shape after being distorted in the preparation of the film, which thus

produces a false appearance of this condition. Fresh specimens are made as follows :—

The patient's finger is pricked, and the drop of blood touched with the centre of a cover glass held in forceps, and this is at once placed on a slide. If both cover glass and slide are perfectly clean, the blood streams out in all directions to the edges. The drop should be only just large enough to reach them. Evaporation is prevented by at once sealing the edges with a little melted vaseline, which may be conveniently painted round with a small camel's-hair brush.

For observing the formation of rouleaux the hanging drop is more suitable, at the edge of which the process may be readily observed. In this case the drop of blood on the cover glass is not allowed to spread out by being brought in contact with an ordinary slide, but is mounted on a hollow slide, the cover glass being held in position by a ring of vaseline.

For making ordinary blood films for stained preparations, it is absolutely essential to use perfectly clean cover glasses. They may be cleaned as follows :—The cover glasses, which should be those known as " $\frac{7}{8}$ inch square, No. 1," are held each one separately in forceps and thoroughly rinsed in chloroform containing about 1 per cent glacial acetic acid. The glass is then well wiped with a smooth linen handkerchief and the rinsing and wiping repeated. It is finally passed ten times through a Bunsen flame. The clean cover slips should be kept dry and protected from dust, but after a few days will require cleaning again before being used for blood-film preparations.

For making blood films some half-a-dozen are placed near the patient. The finger is cleaned and pricked as before described and the first drop of blood wiped away. The moment the second drop appears it is touched with the centre of a cover slip held by one corner between the finger and thumb of the right hand, and this is immediately placed upon another cover slip held in the same way in the left hand. They should be so placed together that their respective corners do not coincide while their centres do. There is no objection to holding the cover glasses between finger and thumb, inasmuch as no part of the film can possibly reach the part so held. If the cover slips and the patient's finger are quite clean, and if the blood has been taken with sufficient rapidity, it at once begins to stream out in all directions. Just before this streaming stops the two glasses are slid, not lifted, apart.

It is most important that the drop should not be so large as to reach in this way quite up to the edges of the glasses. If it does so, the film will either be too thick, or it will be difficult to slide the cover slips apart.

Equally good specimens can be made by another method. A clean cover slip is placed upon a slide just moistened with spirit, or water. All excess of moisture is wiped away, the cover glass adhering to the

slide. The latter is held in the left hand and the top of the drop of blood on the patient's finger is now streaked along the surface of the cover glass close and parallel to its left-hand edge. Directly this has been done, a piece of cigarette paper held in the right hand is placed on the streak of blood and then dragged across the surface of the cover glass, causing the blood to spread out in a thin film. The cover slip can then be removed, and fixed and stained in the usual way. The film can of course be made on the slide itself, instead of on a cover glass.

Fixation.—Proper fixation can only be effected on the wet film. For this purpose saturated mercurial solutions are generally used, and the cover glass treated as a section and never allowed to become dry.

The vapour of formalin fixes the wet film very well. It is most readily employed by pouring some undiluted formalin on to a flat sponge placed at the bottom of a glass vessel with a flat glass plate cover.

The inner surface of the latter is moistened and the cover-glass preparations are laid on it. They adhere to the plate, which is then replaced, and the wet films left exposed face downwards to the formalin vapour for five to ten minutes. They are then removed and allowed to dry.

Fixation of the dry film can be effected (1) by heat, either by baking the preparation for fifteen minutes, at 110° - 115° C., or by passing the cover glass six times through the upper part of the Bunsen flame, just rapidly enough to prevent scorching; (2) by immersing the cover slips in absolute alcohol (five to fifteen minutes) or in equal parts of absolute alcohol and ether (ten to thirty minutes.) They can then be dried and stained.

Staining.—Although for special purposes special processes are necessary, it is far better for all ordinary clinical purposes to select one method and always to use it; by this means only can both normal and pathological specimens be readily compared at any time. For demonstrating the various granules in the white corpuscles, with the exception of mast-cell granules, Ehrlich's tri-acid stain is generally employed. The films are best fixed by heat and then stained for from five to fifteen minutes, washed in water, dried, and mounted in xylol balsam. For many purposes separate solutions of eosin and of methylene blue are used. The films may be fixed by any of the methods described above. They are then stained for one minute in a 0.5 per cent alcoholic solution of Grüber's alcohol soluble eosin, rinsed in water, dried, and afterwards stained for thirty seconds with Löffler's methylene blue. They are again rinsed in water, dried, and mounted in xylol balsam. The fine granules are not stained by this method.

All the various granules, as well as the commoner parasites, bacteria, filariæ, hæmatozoa of malaria, are readily demonstrated by using a 0.5 per cent solution in *absolute* methylic alcohol (E. Merck) of the

compound body formed when watery solutions of eosin and methylene blue are mixed.

The stain can be made by mixing, in a perfectly dry and well-stoppered bottle, $1\frac{1}{4}$ volumes of a 0.5 per cent solution in absolute methylic alcohol of Grüber's water soluble eosin (yellow shade), with 1 volume of a 0.5 per cent solution of Grüber's medicinal methylene blue, also in absolute methylic alcohol. With this stain the specimen should not be previously fixed, the solution being poured straight on to the dried film. The specimen is covered with a watch glass to prevent evaporation. In from one to three minutes the stain is poured off and the cover slip well rinsed in distilled water, dried without heat, and mounted in Grüber's xylol balsam. Unless the balsam is dissolved in the purest xylol, fading of the preparation results. Overstaining can be removed by rinsing the specimen a second time in distilled water, after it has been dried.

The red cells are stained terra-cotta, nuclei blue, platelets grayish-blue, fine granules red, eosinophil granules bright rose-red, mast-cell granules dark violet, parasites blue. To obtain proper differentiation, however, the blood film must be very thin.

LOUIS JENNER.

FIG. 1.

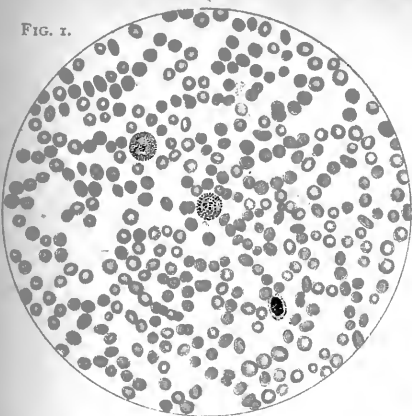


FIG. 2.

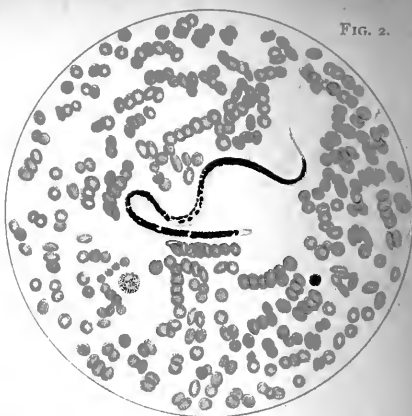


FIG. 3.

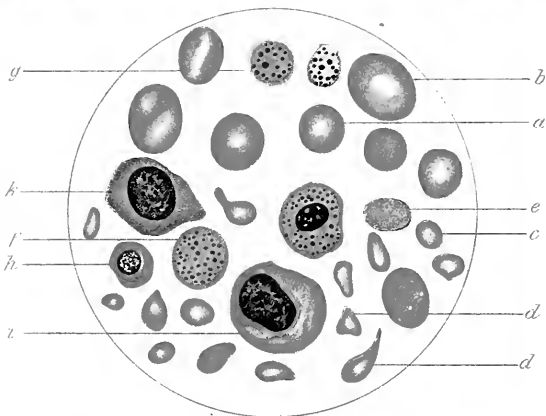


FIG. 4.

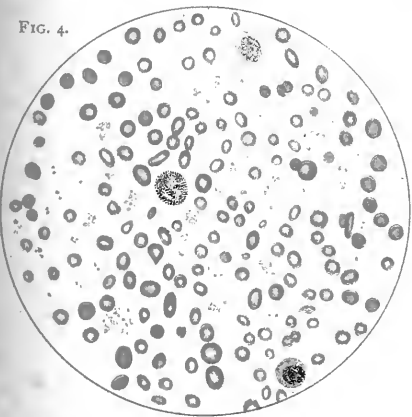
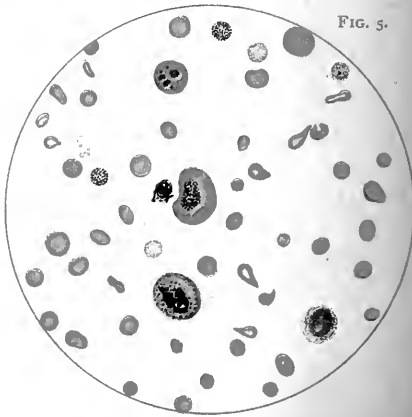


FIG. 5.



ILLUSTRATIONS OF THE HISTOLOGY OF HUMAN BLOOD IN HEALTH AND DISEASE

All the figures are drawn from actual preparations, and the majority of those under the lower magnification ($\times 300$) are from single fields of the microscope. The two figures under the higher magnification ($\times 1000$) are composite pictures.

All the specimens were prepared by the two-cover-glass method, and were fixed and stained with a 0.5 per cent solution of Eosin-Methylene Blue in Absolute Methylic Alcohol, as described in the text.

PLATE I.

FIG. 1.—*Normal blood.* The preparation shows, besides the red corpuscles stained a terra-cotta colour, three small collections of platelets stained a grayish-blue, and three leucocytes; the uppermost is a finely granular oxyphil (polymorphonuclear neutrophil), the central one is a coarsely granular oxyphil (eosinophil), and the lowest is a small hyaline cell (lymphocyte).

FIG. 2.—Shows an *embryo of filaria nocturna* from a case of obstruction of lymphatics. There is some rouleaux formation of the red corpuscles.

FIG. 3.—Composite picture of normal and abnormal *varieties of red corpuscles.*

- (a) A normal red corpuscle.
- (b) An abnormally large red corpuscle (megalocyte).
- (c) An abnormally small red corpuscle (microcyte).
- (d) Illustrate poikilocytosis, or irregularity in shape of the red corpuscles.
- (e) A red corpuscle showing polychromatophilic change.
- (f) A red corpuscle showing granular degeneration.
- (g) A red corpuscle showing both polychromatophilic change and granular degeneration.
- (h) A normal nucleated red cell (normoblast).
- (i) A megaloblast.
- (k) A megaloblast showing polychromatophilic change.

FIG. 4.—Blood from a case of *chlorosis*. Shows a deficiency of hæmoglobin and some variation in size in the red corpuscles, most of these having very pale centres. Large numbers of platelets stained a grayish-blue are scattered over the specimen. Two hyaline cells and one finely granular oxyphil are also in the field.

FIG. 5.—Blood from a case of *pernicious anæmia*. Shows great deficiency in number, and variation in size and shape, of the red corpuscles (poikilocytosis). In the centre of the field is a megaloblast, and next to it, on the left, what is probably a degenerating normoblast, the body of which is polychromatophilic. Farther to the left is a red corpuscle showing granular degeneration. In the upper part of the specimen is a red cell showing fragmentation of the nucleus, and in the lower part a megaloblast showing early fragmentation of the nucleus, polychromatophilic change, and granular degeneration. There is one hyaline leucocyte in the lower right-hand part of the field; four red corpuscles which show polychromatophilic change are present.

PLATE II.

FIG. 1.—This specimen illustrates *pathological leucocytosis*, there being a well-marked increase in the number of finely granular oxyphils (polymorphonuclear neutrophils). Three groups of platelets and one small hyaline leucocyte (lymphocyte) are also seen.

FIG. 2.—Blood from a case of *malaria*. There are three intracorpuseular parasites containing pigment granules, and two finely granular oxyphil leucocytes present in the field.

FIG. 3.—Composite picture of normal and abnormal *varieties of leucocytes*.

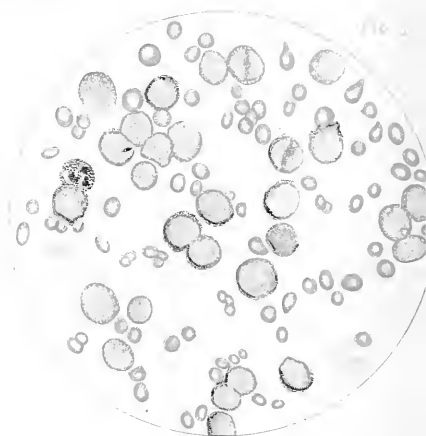
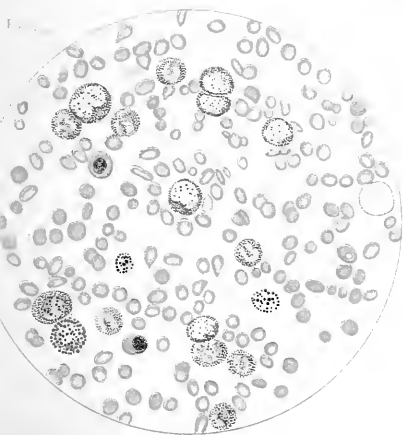
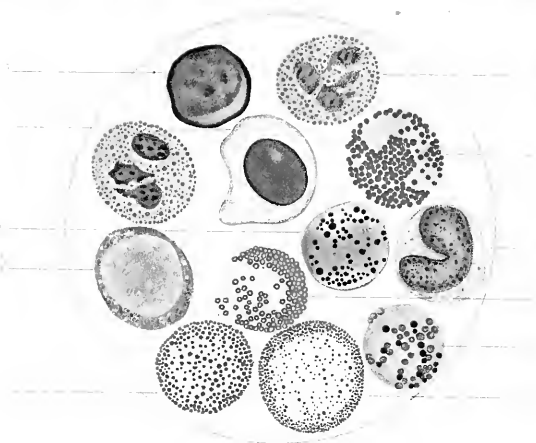
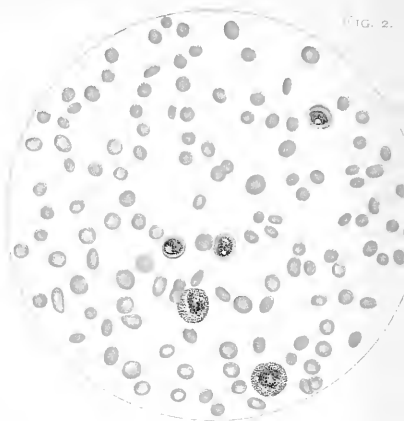
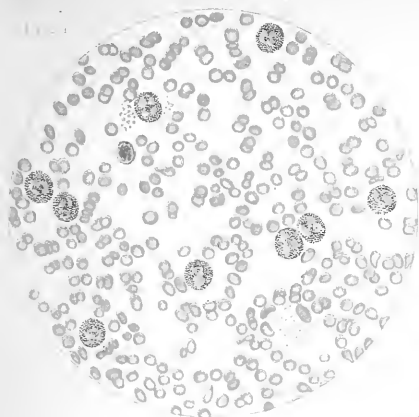
- (a) A finely granular oxyphil (polymorphonuclear) leucocyte.
- (b) A coarsely granular oxyphil (eosinophil) leucocyte.
- (c) Myelocytes.
- (d) An eosinophilous myelocyte.
- (e) A leucocyte with mixed granulations.
- (f) A basophil cell (mast cell).
- (g) A small hyaline cell (lymphocyte).
- (h) A large hyaline cell (large lymphocyte) showing a considerable number of vacuoles.
- (i) A large mononuclear leucocyte (also called a large hyaline cell).
- (k) A transitional cell.

FIG. 4.—*Splenic myelogenous leukaemia*. This specimen shows a great increase in the number of leucocytes. In the centre of the field is a myelocyte; four more of these cells are seen in the upper part of the specimen and three in the lower part; of these latter the cell which occupies the lower position on the left-hand side is an eosinophilous myelocyte. Two basophil cells (mast cells) are also in the lower half of the specimen, and on the extreme right of the figure is a large lymphocyte. There are besides eight finely granular oxyphils, two nucleated red cells (normoblasts), and two polychromatophilic red corpuscles.

FIG. 5.—*Lymphatic leukaemia*. This specimen also shows a great increase in the number of leucocytes, but here the increase is in the hyaline cells (large lymphocytes) many of which show vacuolation. There is one finely granular oxyphil present. In the lower half of the Fig. are four indefinite bodies stained a grayish-blue colour. These are large lymphocytes which have undergone destruction in the preparation of the specimen.

L. L. J.

FIG. 2.



DISEASES OF THE BLOOD

GENERAL PATHOLOGY AND ETIOLOGY

The special office of the blood as the circulating medium whereby oxygen and nutriment are conveyed to tissues and organs, and the waste products of tissue metabolism are carried away to be excreted from the body, renders it almost impossible to frame with any clearness of definition a scheme of its pathological changes. For, in a sense, the blood shares in every departure from normal function that is undergone by any and every organ of the body, and the Hippocratic doctrine of humoralism, which sought to explain all diseases by alterations in the fluids themselves, was after all but the reverse of the actual sequence of events. To the humoralist the blood changes were primary and essential; to the pathologist of to-day they are known to be in most cases entirely secondary and subsidiary. Nevertheless we do still recognise the occurrence of changes in the composition of the blood, which, if not arising directly in the circulating fluid itself, seem to be initiated by derangements of the organs immediately concerned in the manufacture of blood, or rather of its chief elements. It is these conditions to which the term "diseases of the blood" strictly applies, and it is of them that this section will treat.

Paradoxical as it may appear, it is nevertheless a physiological fact that whilst undergoing continual change the blood remains of an almost constant composition. Thus the quantity of the blood itself (1:13 of body-weight); the proportionate amount of fluid it contains and of solids (sp. gr. 1.055); the nature and proportion of each of these latter constituents; the number of corpuscles; the amount of hæmoglobin, can be set down as constituting the normal blood, and this notwithstanding that every meal brings fresh and abundant supplies, every act of secretion, of muscular, nervous, or other function draws on these supplies and exchanges for them waste products which require to be speedily eliminated if the mechanism of the body is to go on smoothly. Considering the numberless opportunities that arise within the body itself for overloading the blood on the one hand, or overdraining it on the other, the marvel is that its composition should remain so stable, or rather that it is not infinitely more variable than it appears to be. For it

is of course variable, but it varies within comparatively narrow limits, and when these are passed, when, that is, the state of the blood crosses the border line between health and disease, the transition is marked by the disturbance that is necessarily caused in the functions of the body.

It may here be remarked that it is hardly possible to treat of the morbid changes of the blood in the same systematic fashion that we speak of the pathological processes that are met with in the organs and tissues. In the latter we find and are able to classify morbid changes under such heads as inflammation, hypertrophy, atrophy, neoplasms, and the like, because they have as their basis an anatomical element—the cell—to which all these processes can be referred. But, although it is sometimes customary to speak of the blood as a “fluid tissue,” any attempt to discuss its pathology on the same lines as the pathology of the “fixed tissues” at once manifests the inadequacy of the comparison. Thus supposing, as is indeed quite legitimate, that we regard the blood corpuscles as homologous with other animal cells, and the fluid medium, impregnated with albumin and salts in which they float, as representative of the intercellular substance of the tissues, we shall find that when the comparison is pushed farther, and we attempt to speak of conditions of excess or deficiency of the corpuscular elements in the terms of cellular pathology, that we are on uncertain ground and likely to lose sight of the true conception of the blood and its office. For this reason it is better to abandon any attempt to homologate the morbid states of the blood with those of the tissues, but to deal with them apart, discussing their relationship to other morbid changes without reference to the pathological processes disclosed by the study of the anatomical alterations undergone by the fixed tissues in disease. Another very material difference between the fixed tissues and the blood is that the former are under the direct control of the nervous system, whereas the latter is only indirectly influenced by its action upon the processes of nutrition in general and of the hæmopoietic organs in particular.

Recognising, then, that any departure from the normal average composition of the blood is to be considered as pathological, the first endeavour must be to ascertain in what ways such conditions are brought about. Here we have often to speak without accurate knowledge, and to deal to some extent in surmise, not, however, wholly apart from a basis of scientific fact: the reason being that it is precisely in regard to the more intimate relationships of the blood to the various functions of the body that physiology is most silent.

The general plan is sufficiently well understood, the mechanism of digestion and absorption, the destiny and changes of the food-stuffs, of the inspired oxygen, the metabolism that subserves nutrition, the physiology of secretion and excretion, and so on; but to specify precisely where the fault lies for an abnormal state of the blood is seldom practicable, and is often largely a matter of inference and speculation, even in states of pronounced abnormality, as, for example, in diabetes, the intimate pathology of which can hardly yet be regarded as determined.

By far the most common of the abnormal or pathological states of the blood is that of impoverishment or "denutrition," as it may be termed. This may concern the blood as a whole, involving a diminution in its mass as well as in its quality. Such a condition, known as *oligæmia*, is, however, of rare, and probably in any case, of but temporary, occurrence. It may conceivably arise in inanition, in grave disease of the assimilative organs, and from great losses of fluid, whether of the blood itself or of secretions and fluxes, as in cholera; but owing to the rapidity with which osmosis from the tissues takes place, it is doubtful whether a true *oligæmia* can exist except transiently. Certainly this may ensue from a sudden and profuse hæmorrhage, when death occurs from the heart being deprived of its natural stimulus, namely, a sufficiency of blood upon which to contract. But even in cases of hæmorrhage, the natural safeguard against such a fatality is sometimes to be found in the rapidity with which the vessels become refilled with fluid transuded from the tissues, albeit fluid of such a character as to be incompatible with the ultimate due performance of vital functions. The efficacy of saline transfusion in averting immediate death from hæmorrhage by restoring the circulation, depends upon its removal of this state of *oligæmia*. At the same time, although a true *oligæmia* is probably a rare event, the condition which it evokes, which indeed must of necessity follow, is that of *hydræmia*, whereby the volume of blood is restored by proportionate increase in the amount of a watery serum. The blood, however, has suffered appreciably in its quality, perhaps beyond the capacity of the organism to restore its normal composition within the time that is required for the maintenance of the normal functions; it is impoverished in all its constituents except water, and hence it may be said that *hydræmia* cannot exist apart from a concomitant *anæmia*, and that to so profound a degree as to be incompatible with the continuance of life.

Strictly speaking, the term "*anæmia*" is used to denote one

particular kind of blood-poverty, namely, a deficiency in the total amount of hæmoglobin, which may be brought about in many ways; but it is important to recognise that, although lack of hæmoglobin is the essential factor in anæmia, this is frequently, indeed perhaps invariably, associated with a diminution in other constituents of the blood. It is not yet possible to make any artificial (or natural) division of the anæmic state, although there can be little doubt from what is known of its varied antecedents it must sometimes be specially linked with a drain of the albuminous constituents, at other times with diminution in the saline constituents or their relative proportions, at others with lack of the fibrin factors, and so on. "Anæmia" is a generic term, and in the vast majority of instances where it occurs is symptomatic of pathological changes in some of the organs of the body. Its antecedents are very numerous and it may be useful to briefly indicate those which are most commonly recognised.

Causes of Anæmia.—The condition of anæmia is perhaps the most common of all the symptoms of disease, and it occurs in every degree of intensity down to a limit that is no longer compatible with the maintenance of life. It would require much space to discuss in detail all the circumstances under which this impoverishment of the blood takes place, but most of the known causal conditions are capable of being grouped together in respect to the manner in which they severally operate. It must, however, be borne in mind that there are great differences in regard to what may be deemed as sufficient and adequate causes to the production of anæmia, differences depending often upon individual and inherited proclivities. Taking these into consideration, we are, according to our present knowledge, enabled to distinguish (1) cases of *secondary* or *symptomatic* anæmia from (2) cases in which, from lack of evidence as to the existence of an adequate cause, the condition has to be referred to some deep-seated change in the mechanism of blood formation or blood destruction. These latter are (provisionally) termed the *primary* anæmias, and constitute what may be termed the anæmic group of blood diseases.

An *insufficient or improper supply of food* is so obvious a cause of anæmia as hardly to need mention. The blood shares in the general lack of nutrition, and as in infancy and childhood the needs of the organism are greatest, so it is in the early periods of life that causes like this are so speedily and markedly followed by the anæmic state. Indeed, there is a very close relationship between the quality of food and the condition of the

blood, as is especially seen in the scorbutic diseases and in rickets, of which anæmia is a prominent symptom. Reference will have to be made to these affections later, for in them anæmia is not only a concomitant but also a consequence of the vascular and nutritional lesions which characterise them. But the fault may not lie so much in the kind of food as in the *incapacity of the organs concerned in its digestion and assimilation*, which leads to the same result of inanition. All grades of anæmia are to be met with in the subjects of these disorders proportionate to the extent with which these necessary functions are impaired. Anæmia is both known to cause dyspepsia as well as to result from it, whilst in grave organic disease of the stomach the most profound anæmia may be established. As regards the absorptive system, perhaps no more striking example can be given than mesenteric disease, or tuberculosis of the abdominal glands. But here, as in the case of malignant disease, other factors, such as pyrexia and hæmorrhage, may co-operate to intensify the anæmic state. In fact there are few cases of secondary anæmia in which the blood condition is due to but a single cause. Thus inanition, which by itself suffices to impoverish the blood, is rarely to be found apart from other anæmiating conditions, such as life amid unhealthy surroundings, deficiency of light and air, undue strain of body or mind, or perchance the existence of organic disease. Some of these conditions are such as involve a drain upon the blood already too poorly reinforced by new material, so that the resulting anæmia depends upon a failure to compensate for loss which, under more natural and healthy conditions, might readily be effected. Even under the most favourable circumstances, however, the recuperative power of the blood may be insufficient to make up for losses, which brings us to consider in what ways the blood may be deprived of its chief elements.

Foremost in the series of causes of anæmia due to drain of blood or its constituents is that which has already been mentioned as producing oligæmia, with the consequent hydræmic state. *Hæmorrhage*, if sufficiently large, whether traumatic or spontaneous, external or internal, must necessarily produce anæmia, the occurrence of which, conjoined with syncope from arrest of the cerebral circulation, may be the main indication of the fact. Recovery from the state of acute anæmia that is caused by a sudden and profuse hæmorrhage takes place more rapidly in some individuals than in others. As a general rule such restoration is more readily effected in the female than in the male sex, possibly because their organisation is habituated

to periodical losses. The process of this recuperation consists in the activity of the blood-forming organs, especially the bone marrow, which seems to be evoked or stimulated to increased effort by the mere fact of hæmorrhage. It is interesting to note that one of the first effects of a hæmorrhage upon the corpuscular elements is the occurrence of leucocytosis, but day by day the richness in red corpuscles increases until the normal standard is attained. Experiments have shown that a blood loss amounting to about one-third of the total quantity requires eight to fourteen days for complete restoration to be effected. But this recuperative activity is not limited to cases of acute anæmia. There are many conditions of more or less persistent anæmia, due to small, but frequently repeated bleedings, as in hæmorrhoids, uterine or gastric hæmorrhage, epistaxis, etc., where the regenerative capacity of the hæmopoietic organs seems to lag behind the losses caused by the continual repetition of the drain of blood. Sometimes, indeed, the latter gain the mastery, and the anæmia becomes not only chronic but progressive.

There are other ways in which the blood may be drained besides those involving an actual outpouring of the blood itself. Thus anæmia of a pronounced character may ensue from the losses entailed by *continued suppuration*, by *intestinal discharges*, as from chronic diarrhœa or dysentery, or by *chronic albuminuria*. In these conditions other factors may co-operate to the same end, for suppuration may be accompanied by pyrexia and by lardaceous disease. Indeed, *pyrexia per se* must be accepted as sufficient to produce anæmia, the blood sharing in the pyrexial process just as the other tissues; but it is not possible to determine the precise share this takes in any given case, for "fever" has at its root some toxæmic state which may be far more responsible for the blood destruction than the pyrexia that denotes its presence. At the same time there seems to be no doubt that some "*infections*" do act more directly upon the blood than others. In respect to one of them, malaria, this action has been established by the discovery of the hæmatozoic organism, which is not only a blood parasite, but especially attacks and destroys the red corpuscles. And although such direct evidence of the destruction of the hæmoglobin-carriers may be wanting in other diseases, yet the fact of their having some specific anæmiating influence can hardly be doubted, especially such diseases as tuberculosis and syphilis, both of which are so commonly marked by a degree of bloodlessness often quite out of proportion to the supposed effect of the local manifestations of these diseases, or of the pyrexia that may accompany them.

Nor is the catalogue of what may be termed the toxæmic antecedents of anæmia exhausted by reference to the specific fevers, which arise, as we believe, from the introduction into the body, and therefore into the blood, of the microbe or toxin that is peculiar to each of them. This microbe may not, as in malaria, cause the anæmia by direct disintegration of corpuscles, yet may operate almost as potently through the action of the toxin it produces, and in varying degrees, depending probably upon the special nature of the toxin and possibly also upon its amount, for the intensity of the anæmia in cases of typhoid fever, diphtheria, ulcerative endocarditis, to name only a few, is by no means always the same in all cases. There are also toxæmias which do not appear to be caused by the introduction of poisons or their generators from without, but which depend upon chemical changes within the body. Such are the conditions somewhat clumsily termed "*auto-intoxications*," many being of gastro-intestinal origin, and dependent upon derangements in the processes of digestion, gastric or intestinal, and also the series of derangements in the inner chemistry of the body of which gout is the ultimate expression. These are conditions which, although often blended with some to which reference has already been made, both in respect to impoverishment of blood by defect of supply and of undue waste, serve to increase the anæmic state by a more directly noxious action upon the blood itself. Lastly, there is ample evidence of the directly poisonous influence upon the blood of certain *mineral substances*, amongst which *lead* stands forth as the most common and the most striking example.

Reference has been made above to *malignant disease* as a cause of anæmia. Cancerous and other neoplasms have long been credited with the production of a specific "*cachexia*," and the question is still undetermined whether this is really specific; induced, that is, by a toxic agent peculiar to cancer acting directly upon the blood, or whether the cachexia depends rather upon the site and extent of the neoplasm. Certainly the most intense forms of anæmia in malignant disease are those in which the growth involves organs essential to healthy nutrition, *e.g.* stomach and abdominal glands, and those cases where the progress of the disease leads to ulceration, with consequent hæmorrhages and discharges. If these obvious effects of a malignant growth be set aside, there still remains a certain proportion (it may be doubted if this applies universally) of cases in which the mere presence of the neoplasm and its increase has a markedly deteriorating action upon the blood as a whole.

It may be of interest to state here to what degree of blood

poverty the term "anæmia" should be applied. This cannot be more summarily given than it was by Dr. S. Mackenzie in his Lett-somian lectures (1891), where he makes the following classification : — "Anæmia commences at 80 per cent, *i.e.* 4,000,000 red corpuscles per cub. mm.; it is decided between 65 and 50 per cent, *i.e.* 3,250,000 to 2,500,000; grave at 50 per cent, *i.e.* 2,500,000; very grave at 35 per cent, or 1,750,000; and fatal at 17.5 per cent, *i.e.* 375,000 per cub. mm."

The foregoing by no means exhausts the category of recognised antecedents of secondary or symptomatic anæmia, for the condition is perhaps the most universal of the signs of disease, local or general. We have merely indicated the chief directions in which these antecedents are to be sought for, and endeavoured to show that they may be held to operate either by (1) *interfering with the formation and renewal of the blood*, or (2) *causing a drain upon it which the system is unable to supply*, or (3) *directly or indirectly acting destructively upon its chief elements*. Such in sum and substance may be said to comprehend all the known causes of anæmia, but it cannot be too strongly urged that in any given case the causes are more often complex than simple, and that really but little is known concerning the precise manner in which they operate. That there are organs which have the special office of renewing the corpuscular elements throughout post-natal life, and that these may be themselves deranged and thus lead to the anæmic state, is of course obvious, but when we inquire what are the agencies that pervert the function of these organs, and what are the pathological changes to which the latter are prone, it is remarkable how little is actually demonstrated in regard to them. Indeed, so far as pathological anatomy teaches, time has shown that some of the changes once thought to be primary in these organs, and to be related to the blood state which existed during life, may with greater reason be regarded as due to this blood deterioration, the real cause of which is still to seek. Nowhere has this been better exemplified than in that obscure affection pernicious anæmia, in which very marked lesions of the bone marrow are present. When first described these changes were considered to afford a clue to the mystery shrouding the origin of this affection. But wider research has relegated them to a subsidiary place, marking rather the effects than the causes of the blood disease. Nevertheless, the sources of these blood diseases which still remain obscure, not being of the same character as those which are known and held to be adequate to produce the change, may eventually be found to lie within the province of organs and textures concerned in hæmo-

genesis on the one hand and hæmolysis on the other, and if for the present we prefer to style them as "primary" rather than "secondary" affections, it must be with the qualification that the former term is provisional only, and one to be used rather as a cloak to ignorance than as stating a definite fact in pathology.

A. THE ANÆMIC GROUP OF BLOOD DISEASES

The two diseases which are generally regarded as examples of "PRIMARY ANÆMIA," *chlorosis* and *progressive pernicious anæmia*, are remarkable for their contrasts. The one is almost wholly confined to the female sex, and especially occurs in the period of early womanhood; it is moreover a very common disease. The other is quite as frequently met with in men as in women, and is most common about the period of maturity, although cases do occur in the very young and the very old; it is moreover a relatively rare affection. Recovery from *chlorosis* is the rule, and the influence of medication upon its course is striking. *Pernicious anæmia*, as its name implies, is almost invariably fatal, and although its course may be varied by remissions, treatment has not been able to do much to avert this termination. Yet in each of these diseases there may, in the history of the case, have been present more than one of the recognised etiological factors of anæmia, which, however, are not adequate to produce the special characters of either affection. Hence the endeavour to discover what is the determining cause in each case, which gives the particular impress of the disease. In the matter of *chlorosis* many explanations have been offered. Its sexual character and the time of life at which it chiefly appears have led to attempts to relate it to ovarian or uterine derangement, or the menstrual function. Defective development of these organs has indeed been found to co-exist with a like "hypoplasia" of heart and blood-vessels in some of the few instances in which post-mortem examinations have been made on the bodies of chlorotics; and the great authority of Virchow, who was the first to make such observations, is responsible for a theory which would relegate *chlorosis* to the ranks of congenital diseases. But neither imperfection in the due performance of the menstrual function nor structural defect from lack of normal developmental changes can apply to explain this disease, which may certainly arise independently of uterine disorder and in subjects who, apparently at least, present no indications of imperfect development; whilst the argument from the efficacy of well-directed ferruginous medication

seems to be quite unanswerable as opposed to there being any permanent anatomical condition at the root of the malady. Less open to criticism is the view advanced by the late Sir A. Clark that chlorosis arose from an "auto-intoxication" due to fæcal retention, a view based on the frequent concomitance of constipation and the beneficial effect of measures directed to the relief of this symptom. But constipation, although a frequent, is not an invariable antecedent, and it is certain that purgation *per se* is no remedy for chlorosis. Other and more refined hypotheses are current which bear more on the inherent constitution of the blood in chlorotic subjects, and it is plain that there is great uncertainty about its exact pathology.

The most markedly characteristic features of the disease as regards the blood are (1) a relative insufficiency of hæmoglobin, and (2) the readiness with which this defect is made up by a course of ferruginous medication. Not that in either of these respects is it possible to assert that some forms of secondary anæmia may not closely approximate to chlorosis, but it may with confidence be stated that in few, if any, other conditions of bloodlessness does there exist such a disproportion between the percentage composition of corpuscles and of hæmoglobin as here exists. Anæmia, as ordinarily exhibited, is due to a quantitative change in the corpuscles; in chlorosis it is a qualitative alteration. Assuming the average number of red corpuscles to be 5,000,000 per cub. mm., with a hæmoglobin standard of 100 per cent, the rule in chlorosis is to find a disproportionate deficiency in the hæmoglobin; and although very probably there is some reduction in the number of corpuscles, this is exceeded by the reduction in amount of colouring matter. Thus the corpuscular richness may have fallen to 80 per cent of the normal average, whilst the hæmoglobin will be only 40 or 50 per cent of the normal. The "colour-index" or individual richness in hæmoglobin of each corpuscle will therefore be $\frac{50}{80}$ or $\frac{40}{80}$, *i.e.* 0.6 or 0.5, instead of $\frac{100}{100}$ or 1.0, whereas in secondary anæmia this index remains at 1.0, and in pernicious anæmia even exceeds this. It is only fair to admit that although this condition obtains in the majority of cases of chlorosis, it does occasionally happen that there is a very considerable reduction in the number of corpuscles, but so far from these exceptions setting aside the criterion of chlorotic blood, it would be justifiable to regard them as due to some complicating influence upon blood formation. The clinical and therapeutical grounds upon which chlorosis is rightly separated from other anæmias may thus have pathological support, although much remains to be done before exact knowledge of its pathology can be arrived at. It does seem,

however, as if in this disease there is a defect in hæmogenesis, whereby the red corpuscles are unable to take up their normal amount of hæmoglobin.

It is otherwise with *pernicious anæmia*, a disease that is prone to occur at any period of life, most frequently in the middle-aged of both sexes, and is by no means limited to those who live under unwholesome conditions, whether of diet or hygiene. As compared with chlorosis this is a rare affection, and also a very fatal one, although its downward progress may be interrupted by remissions of considerable duration. Again, as in chlorosis, so here, the history of the attack may afford information of exposure to more than one of the conditions commonly regarded as adequate to the production of anæmia, and yet not sufficient to impress upon it the special characteristics of this disease. An examination of the blood affords some clue as to the pathology of the affection, not yet, however, fully elucidated. The blood changes consist essentially in a progressively continuous fall in the number of red corpuscles, with a high colour-index, indications of their disintegration and of imperfect attempts at repair. At one time regarded as a disease of blood formation, and even spoken of as "myelogenous anæmia," to which the striking abnormality of the marrow lent support, it has come to be regarded with more reason as a condition of *excessive hæmolysis*, whereas chlorosis is one of *defective hæmogenesis*. It will be seen how the morbid appearances of the various organs of the body support this hæmolytic hypothesis, but pathology should afford a reasonable explanation for the condition, which may conceivably be brought about in more than one way. Thus it might be assigned to perversion of the functions of organs concerned in blood destruction, *e.g.* the spleen and liver; but such changes as have been described in these organs are rather of the nature of effects than of causes; or it might be brought about by repeated blood loss, inadequately made up for by the hæmogenetic organs, but here there is lacking evidence of such hæmorrhage except as a late clinical feature, or as caused by the duodenal parasite *ankylostoma*, which does indeed lead to a fatal and progressive anæmia closely analogous to pernicious anæmia. Toxic agencies, whether due to bacteria or to intestinal parasites (*bothriocephalus*), or to gastro-intestinal derangement, have severally been credited with the production of the blood destruction, and on the whole the last-named hypothesis, so ably advanced and supported by Dr. W. Hunter (recently extended by him to infection derived from the oral cavity) is the one which has most to be said in its favour.

There is one affection, as yet somewhat ill-defined, which should be mentioned in connection with these primary anæmias, and that is so-called *splenic anæmia*. The precise nature of this affection is yet undetermined, and it seems probable that under this term are included more than one distinct condition. The most intelligible form is that which runs a chronic course, which is characterised by a progressive enlargement of the spleen, accompanied or not by symptoms present in leukæmia, but lacking entirely in the distinctive feature of that disease, leucocytosis. Nor is it essential that the anæmia, albeit progressive, should be profound. These are the cases in which splenectomy has been practised with success, thereby contrasting markedly with leukæmia, in which that operation has invariably hastened a fatal termination. Indeed it is maintained that by splenectomy alone can the disorder be arrested, for if this organ be not removed it continues to grow, and the patient, with increasing debility, at length dies of exhaustion. The condition of the spleen is said to be characteristic, and to be totally different from that of leukæmia or Hodgkin's disease. Although much enlarged, it is firm in texture, microscopically shows great overgrowth of the trabecular framework, at the expense of the lymphoid tissue and Malpighian bodies. Such a condition has been called "splenomegaly," and the correct place of it in nosology should be amongst diseases of the spleen, to which the blood state is obviously secondary. However, the subject is not quite so simple—for allied with the form described are others which run a more acute course, marked by pyrexia, a rapidly progressive anæmia, with tendency to hæmorrhages, which may prove fatal. Again in children, especially, there are cases of anæmia with enlarged spleen, some of which are associated with rickets, others with syphilis, but yet others in which no such connection can be traced. Yet so far as one can gather from published writings, the condition first described by Von Jaksch in 1882, under the title, "Pseudo-Leukæmia Splenica infantum," embraces these instances of rachitic and syphilitic splenomegaly with anæmia. This is not the place in which to enter into a full discussion of a vexed question, but there is no doubt that at the present time the term "splenic anæmia" is being used to embrace very different conditions, some doubtless primarily dependent upon splenic disease, others in which both spleen and blood suffer from some underlying toxæmic state, just as the post-malarial bloodlessness would be termed "splenic anæmia."

Allied to conditions in which blood poverty is linked with

splenic enlargement is the more familiar affection in which spleen and lymphatic glands, especially the latter, are involved. To this affection various names have been applied, such as lymphadenoma, lymphatic anæmia, adenia, pseudo-leukæmia lymphatica, and *Hodgkin's disease*, after its discoverer. Here we shall adhere to the latter term, which involves no theory. It is characterised by a state of anæmia accompanied by overgrowth of lymphatic glands, and often of lymphatic tissues elsewhere, as well as by enlargement of the spleen, with the formation in it of masses of lymphoid growth which give to the organ a peculiar appearance. The lymphatic glands are mostly hard, yellowish-white, and never caseous, thereby unlike the tuberculous glands, but sometimes they are softer and instead of being discrete are confluent, infiltrating after the manner of malignant growth. Indeed in such cases it may be difficult except from the antecedent history to discriminate between this affection and lymphosarcoma and lymphoma maligna.

From this disease, which, in so far as the composition of the blood is concerned, must be regarded as one of anæmia, the transition is easy to the state of *leucocythæmia* or *leukæmia*, of which two varieties have been clearly established. Leukæmia must be distinguished from leucocytosis, a transitory condition met with in a variety of diseases, and even physiologically, for in the former the blood is permanently affected, the leucocytes being in disproportionate numbers, although varying within wide limits even in the course of a single case. At the same time there is a deficiency in the red corpuscles, which entitles the affection to be ranked with the anæmias. The two types are known respectively as the *spleno-medullary* and the *lymphatic*, the former being characterised by a predominant and progressive enlargement of the spleen, and also (if the prevailing type of blood cells be regarded) by an affection of the bone marrow; the latter associated with enlargement of the lymphatic glands, and the type of white cells being smaller and lymphoid. The spleno-medullary form is by far the more common, and is indeed that which is usually recognised as leucocythæmia, whilst in the lymphatic form the spleen may be somewhat enlarged. Little is known concerning the etiology of leukæmia. Statistics prove it to be more common in the male sex. It is said to have some relationship with malaria, but indeed its antecedents are most varied, none of them affording satisfactory explanation of the occurrence of the excessive production of leucocytes. It may eventually be found to rank with the infective diseases,

although hitherto the attempts to isolate a definite specific microbe have been inconclusive in their result. The cases of so-called "acute leukæmia" run a course which is highly suggestive of such an origin. Judging from its resemblance (clinical and pathological) to chronic infective disorders, it is by no means unlikely that Hodgkin's disease will also be found to have a similar origin.

B. THE HÆMORRHAGIC GROUP OF BLOOD DISEASES

In contrast to the preceding affections, of which a condition of "anæmia" is the main characteristic, we have to consider another group where a tendency to hæmorrhage is the predominant feature. Yet they are linked together, inasmuch as certain of the anæmic group, e.g. leukæmia and pernicious anæmia, are prone to spontaneous hæmorrhages, whilst, on the other hand, a hæmorrhagic or purpuric affection must necessarily lead to a state of anæmia. The fact is here again evident how very deficient our knowledge is respecting the pathology of all these diseases, whereby it is not as yet possible to classify them in such a way as to denote their real affinities. We employ the terms "anæmia" and "purpura" to express substantive conditions, whereas in the vast majority of cases in which they are present they are mere symptoms and not nosological entities; and this compels the belief that with deeper knowledge the few conditions to which these terms are applied in the sense of primary affections will be shown to be dependent upon some antecedent, and will give rise to a new nomenclature based on their true pathological relationships. These remarks apply with as much, and even more force to the hæmorrhagic group of diseases of the blood than they do to the anæmic group. For under the term *purpura* is collected a vast congeries of pathological states—which, however, have this in common, namely, that in them the blood escapes from its natural channels into the surrounding tissues. In most cases this escape is no doubt caused by rupture of capillary vessels, due in the main to their defective nutrition, aided perchance sometimes by undue vascular tension; but the escape of blood may sometimes be effected without any actual breach of continuity of the containing vessels, by the operation of diapedesis. There are some cases in which, through the vaso-motor system, localised disturbances of the circulation arise, accompanied by purpuric phenomena, and it is in such that it is difficult to believe that vessels are actually broken. The most remarkable examples of this neurotic purpura are those which have sometimes occurred among

religious fanatics who periodically exhibit on their own persons the "stigmata" of the Passion. The notorious case of Louise Lateau, which attracted much attention some twenty years ago, is of this order. She was a young Belgian devotee who from time to time exhibited these stigmata, whilst in a state of extreme hysterical ecstasy. Other similar cases are on record, but it would appear that instances of neurotic purpura may also be met with in organic nervous diseases, *e.g.* in tabes.

Setting aside these instances of the escape of blood from vessels which are to be ascribed to local derangements of circulation through nervous influence, and reverting to the main body of the "purpuric affections," it is yet a matter of uncertainty as to whether the blood itself is primarily at fault or whether the condition of the blood-vessels suffices to account for the phenomenon of their spontaneous rupture. The fact is no doubt that in some cases the latter alone is responsible for the hæmorrhage. It is so in senile purpura, where vascular degeneration is as much the cause of these minute hæmorrhages as it is of the graver and larger extravasations. Again, in chronic cardiac valvular disease, especially in its advanced stages, purpura is by no means infrequent, especially in the lower extremities, as one of the evidences of the mechanical difficulties of the circulation. These cutaneous petechiæ or vibices have their homologues in the minute subserous ecchymoses that stud the pericardium and pleura in death from asphyxia, and they may have a similar pathological explanation. We know also that purpuric extravasations may result from capillary embolism, as in ulcerative endocarditis, in which case the hæmorrhagic foci are by no means limited to the surface of the body, but may be found in all parts of the capillary circulation. It is probable, but not proven, that in the former (asphyxial) conditions, just as in the latter (embolic), the hæmorrhages would not have occurred unless some deterioration of vessel wall had first taken place. Such deterioration does undoubtedly occur in other conditions, *e.g.* those of pernicious anæmia and leukæmia, where capillary hæmorrhages not seldom occur, and in the obviously toxic forms of purpura, of which that produced by the administration of iodides is a salient example; but, clearly, in these instances the vessel walls would not have suffered if the composition of the blood had not itself been first altered. In most of the exanthemata and other infectious fevers there are severe forms, which, from their intense and lethal character, are termed "malignant," in which hæmorrhage is the marked feature. Hence we speak of hæmorrhagic smallpox, hæmorrhagic measles, hæmorrhagic scarlet fever, and so on, whilst

in typhus fever the exanthem itself is petechial. In all these diseases, which in their most fatal forms exhibit also hæmorrhages from mucous surfaces, from the lungs and from the kidney equally with hæmorrhages from the skin, we must look to blood change as the primary factor. It can hardly be that the hæmorrhages are due to mechanical obstruction of capillaries by microbes, for in many of these diseases as yet no specific microbe has been isolated; but that the specific toxin circulating in the blood has a profoundly destructive effect upon the vessel walls is highly probable, whilst the fluidity of the blood after death, long known to mark such malignant fevers, may indicate that the quality of the fluid itself is such as to favour hæmorrhage. The most severe form of primary hæmorrhagic disease—that known by the tautologically absurd name of “*purpura hæmorrhagica*,” but better styled “*malignant purpura*”—seems allied in its nature to the specific fevers and cerebrospinal fever. In it there are hæmorrhages of extreme degree and extent, internal as well as cutaneous, and the presence of micrococci in the blood-vessels still closer approximates it to infective or septic diseases. For purpura is known to occur in septic affections, being frequent in septicæmia and in pyæmia, in which latter, possibly, as in ulcerative endocarditis, capillary embolism may be the cause of the hæmorrhages. Of less serious import, and yet perhaps in essential nature not dissimilar from the grave diseases just enumerated, is the malady known as “*rheumatic purpura*,” and the affection of children named after its discoverer, “*Henoch’s purpura*.”

But whatever obscurity may veil the etiology and pathogeny of many hæmorrhagic or purpuric affections, there is certainly none regarding that class to which the term *scorbutic* is applied. In those affections (*scurvy* and *infantile scurvy*) the dependence of the blood state upon defective diet is established by the conclusive proof that when such defects are remedied the morbid condition rapidly disappears. It is from the knowledge thus gained that scurvy is no longer the scourge that it once was on land as well as sea, since its occurrence can be prevented by due care in the provision of fresh foods, vegetables, meat, and milk, whilst the very way to induce the scorbutic state is to withhold such articles of diet from consumption. Sea-scurvy is now rarely met with, at any rate in its severe and fatal forms, whereas it once was common enough in the long sailing voyages of the mercantile marine and in Arctic expeditions. Land-scurvy is still a concomitant of famine and distress, especially in time of war in besieged towns or amongst ill-furnished armies in the field. The introduction of lime-juice, and,

still better, of fresh food supplies, have much mitigated the losses due to this disease under adverse conditions. Then, as regards "infantile scurvy," the recognition of which is of quite recent date, the essential cause has been shown to be the deprivation of the infant of fresh milk, for it finds its victims largely amongst those who are hand-fed on artificial foods and condensed milk. It is no doubt owing to its dietetic origin that this affection is often associated with rickets, the earliest recorded cases being described as "acute rickets"; but it is more truly a scorbutic than a rachitic disease, although the site of the hæmorrhage is mainly located around the epiphysial extremities of the long bones.

Although the ultimate factor in these scorbutic affections has been established beyond dispute,¹ there is not so much certainty as to the precise nature of the blood changes to which the hæmorrhages are proximately due. Many opinions have been put forward to explain the intimate nature of these changes, and amongst them that of Sir A. Garrod, advanced upwards of fifty years ago, has in its main thesis remained unshaken. The late Dr. Ralfe, who studied the subject from the side of the urinary excretion, confirmed Garrod's observations as to the diminished alkalinity of the blood in scurvy. It is perhaps noteworthy, as indicative of the trend of modern pathology, that in spite of the overwhelming evidence in support of dietetic defects being the proximate cause of the scorbutic state, some of the most recent writers consider that it will eventually be proved to belong to the category of infective diseases, the conditions of improper food and insanitary surroundings being subsidiary rather than essential, as laying the body open to the infective, and as yet undiscovered bacterial agent. That scurvy was at one time thought to be a miasmatic and even a contagious disorder is described by the eminent epidemiologist A. Hirsch, whose concluding remarks upon the subject represent the prevailing opinion of to-day. He says:—

¹ Since this was written there has been communicated to the Royal Society a paper, entitled "An Experimental Inquiry into Scurvy," by F. G. Jackson and Vaughan Harley, M.D., in which reasons are adduced in support of the view that scurvy is a form of ptomaine poisoning. It is argued that the experience of Arctic expeditions of recent times is opposed to the view of the dependence of scurvy upon the lack of fresh vegetables, but in favour of its being due rather to want of fresh meat. That where explorers have been compelled to live on tinned and preserved meats, scurvy has arisen in spite of lime-juice (Nares and Leigh Smith). Whereas a diet of freshly killed meat, without any lime-juice, has preserved men from scurvy throughout the long Arctic winters (Nansen). The inference that scurvy may be induced by a diet of tainted food is suggested by experiments upon monkeys (see *Lancet*, April 28, 1900).

“Summing up briefly the facts and arguments, I am led to conclude, as regards the genesis of scurvy, that the disease is most of all associated with want of fresh vegetables in the diet, perhaps with the insufficient supply of salts of potash (combinations with the vegetable acids); that it breaks out the more promptly and the more surely the greater the antecedent action of other debilitating things on the organism, predisposing it to sickness; that there are certain other errors of hygiene, for the present not to be more accurately particularised, which induce the disorders of nutrition that underlie scurvy, although they do so much more rarely than the first mentioned; but that there is no warrant to speak of a miasmatic or infective origin of the disease, while a contagious property is to be denied of scurvy in the most absolute terms” (*Hist. and Geogr. Path.*, Creighton’s Trans., vol. ii. p. 561; New Syd. Soc. 1885).

Closely allied to the hæmorrhagic diseases just considered is the condition of *hæmoglobinuria*, in which the colouring matter of the blood escapes into the urine owing to excessive disintegration of the red corpuscles in the general circulation. Normally, of course, there is continually a process of corpuscular disintegration, and the various pigments of the body, especially of the bile and the urine, must be ultimately derived from the blood. But when hæmoglobinuria occurs there must have been some derangement of the slow and measured changes that result in such pigmented products, for the hæmoglobin is set free in the blood itself, staining its serum and passing out with the urinary water. The urine in such a case may be of a dark red, brownish, or even blackish tint; it probably deposits on standing a brownish sediment of granular pigment, sometimes even crystals or hæmatin, but not a single blood corpuscle is to be detected in it. Some of the pigment may be in the form of casts of the urinary tubules. The guaiac test gives an immediate and definite reaction of the presence of hæmoglobin, which is confirmed by spectroscopic examination, yielding the spectrum of oxyhæmoglobin or methæmoglobin. At the same time there may be no serum-albumin but only globulin to be found in the urine. At one time it was thought that the disintegration of the blood corpuscles took place in the urine itself, but this view became quite dispelled with the knowledge of the conditions under which hæmoglobinuria is met with, and also by direct observations of the blood. So that it is certain that a state of hæmoglobinæmia must be the antecedent of hæmoglobinuria. It is now known that this destruction of the corpuscles can be effected in various ways. There are many poisons, organic and inorganic, which

have this disintegrating effect—as, for example, chlorate of potash, the mineral acids, oxalic and pyrogallie acids, naphthol, nitrobenzol, toluyldiamine, quinine, arseniuretted hydrogen, and many others; some toxæmic states, as certain of the infective and septic fevers, and in particular the remarkable malarial disease of the tropics which has received the name of *hæmoglobinuric fever*. It is, further, a noteworthy fact that if the blood of one animal be transfused into the vessels of another animal of a different species, hæmoglobinuria will result, as if the serum of the one had a disintegrating action on the corpuscles of the other. Exposure to great heat or cold may have a like effect, hæmoglobinuria being known to occur in cases of extensive burns and in cases of frost-bite, whilst in the disease known as *paroxysmal hæmoglobinuria* exposure to cold is the usual exciting cause, the disposing condition being an undue delicacy of the corpuscles themselves, which is claimed, with some reason, to be often owing to previous syphilitic infection. It may be remarked in passing that the syphilitic virus would seem to have a special affinity for the red corpuscles of the blood, since not only is syphilis apparently a common factor in the history of paroxysmal hæmoglobinuria, but it is often responsible for a very marked degree of anæmia. The part taken by cold in the production of hæmoglobinuria is also of interest because of the not infrequent concomitance of this symptom with Raynaud's disease, which has led some to think that there is a causal relationship between the two. But, as Dr. M. Copeman points out, the relationship may merely be their dependence upon a common exciting cause—exposure to cold. *Per contra*, paroxysmal hæmoglobinuria has been placed in a category apart from these affections, where hæmolytic agencies, including cold, are alleged to be in operation, and has been regarded rather as the outcome of mechanical disturbances of the circulation from vaso-motor influence, contraction of the peripheral vessels acting upon corpuscles of slight resisting power. In that way the nexus with Raynaud's disease is drawn closer, whilst the divergence from other states of hæmoglobinuria is made more striking.

Amongst the most important pathological processes in which the blood takes part is that of THROMBOSIS or coagulation of the blood within the heart or blood-vessels during life. The actual process, resulting in the formation of fibrin, which habitually takes place in blood that has been shed or in the blood channels after somatic death, can only occur in the vessels during life under conditions which are abnormal. For during life the blood would seem to be

in some measure protected from undergoing this change, for which the necessary factors are present within itself. These factors are (1) the existence of fibrinogen in the blood plasma, (2) of a ferment (thrombin) mainly contained within the leucocytes, and (3) the presence of calcium salts (see p. 285). It may be that the living epithelium that lines the heart and blood-vessels exerts an inhibitory influence which keeps in check the natural tendency of these factors to co-operate, for if this epithelium be injured or altered by inflammation or degenerated, or if a foreign body gain entrance into the vessel, then coagulation is liable to take place *in situ*, and a thrombus is formed. The process in such case starts by the accumulation of platelets at the seat of injury, and the liberation from them of the fibrin ferment. It is also probable that, given certain conditions of the blood itself, or the admixture with it of certain fluids, coagulation may occur within the circulation independently of any lesion of the vascular lining or introduction of a solid foreign substance; at least this would appear to be the case from experiments, although it is seldom possible to refer any given case of thrombosis to such a condition of the blood. Nevertheless it has long been believed that the blood of some subjects is more prone to coagulate than that of others, and terms were introduced to explain what was thought to indicate an excess or deficiency of fibrin, or of its constituents, in the blood. Thus the blood in rheumatic fever (and indeed in other fevers) and in acute inflammations seems to clot very rapidly as compared with the blood of typhus fever and septicæmia, where unnatural fluidity seems to obtain. It is true that we cannot explain the reason for such differences, but this at least can be said, that they do not depend upon any hypothetical excess or deficiency of fibrin, which has no existence as such in the circulating blood. It must be confessed, too, that there are difficulties in the way of explaining thrombosis as it spontaneously occurs in heart or vessels. The most common antecedent of such an occurrence is *stasis* of the blood column, but mere stagnation alone can hardly be deemed adequate to initiate the process of coagulation in healthy living vessels. It is possible that the accumulation of leucocytes, which we know takes place in the sluggish stream, and their adhesion to the lining membrane of the heart or veins in places where stasis is liable to occur, may result in such a change that the inhibiting influence of the lining epithelia is removed and the fibrin ferment enabled to act upon the fibrinogen. Even so the process is limited in its extent, so that in the heart a thrombus which fills the appendix does not extend into the auricular chamber, or one

which occupies a cranny in the honeycombed interior of a dilated ventricle is rounded off where it projects into the main cavity. So too in the case of a vein, where a thrombus, starting, it may be, at the ampullary dilatation above a valve, may extend centripetally until the junction of a collateral branch brings to the main vessel a stream which by its continued flow seems to defy coagulation.

If, then, it be asked what are the conditions which favour and promote thrombosis, it must be said that they are three, or perhaps four, in number, granting always the presence of the fibrin-forming factors. These conditions are—1st, an obstructed circulation tending to stagnation of the blood current. This may arise in the heart itself, as in the auricular appendix in cases of mitral stenosis, or in the meshes of the columnæ carneæ in a dilated ventricle, or in veins and sinuses from general feebleness of the circulation, such as occurs in states of marked exhaustion following severe fevers or prolonged wasting diseases. In such cases local conditions may co-operate to produce thrombosis, which explains the relative frequency of its occurrence in the veins of the lower limbs and in the cranial sinuses. 2nd, an alteration in the lining membrane, such as occurs in the cardiac valves in endocarditis, in the veins in phlebitis (not so common as a primary affection as used to be thought), or the arteries from atheroma, calcification (leading to senile gangrene), endarteritis obliterans, of which the best example is seen in the arterial thrombosis of cerebral syphilis. 3rd, the introduction of foreign material into the circulating stream, whether this lead to obstruction of the vessel or not. And perhaps, 4th, the admixture with the blood of a toxin which, if not itself operative as a fibrin ferment, may induce the liberation of this from the leucocytes that contain it. In fine, it may be said that until the reason is known why living blood does not normally coagulate, it is hardly to be expected that we shall know much of the causal conditions of thrombosis.

Under certain circumstances the blood contains an excess of free fat in the form of minute globules, which, by their agglomeration, may form droplets of sufficient size to obstruct capillaries and small arterioles (fat embolism), an event which has been known to occur after fracture of bones, and in diabetes, where the state of LIPÆMIA is occasionally very marked indeed. Normally the blood contains a small quantity of fat, but in true lipæmia it is in such amount as to give the blood a singular pale pinkish colour, and on standing to form a considerable creamy layer on the surface. Its occurrence

in diabetes seems to be associated with acetonæmia, and most of the cases of pronounced lipæmia in this disease have been those which were fatal from coma, insomuch so that coma was ascribed by Hamilton and Sanders to the occurrence of fat embolism. On the other hand many cases of diabetic coma occur in which the blood is by no means lipæmic; nor has it been satisfactorily explained why it should become so.

Another abnormal condition deserving of passing mention is MELANÆMIA, in which the circulating blood contains particles of pigment apparently derived from disintegrated blood corpuscles. This is most frequently found in subjects who have had malarial fever, and in whose organs much of the pigment is deposited. There is, however, another form of melanæmia which may be associated with melanuria, and that is the condition known as melanosis, characterised by the development and dissemination of sarcomatous growths—melanotic sarcoma, amongst the most malignant of neoplasms.

Occasionally *air* gains entrance into the blood channels—*e.g.* in jugular phlebotomy, or other wounds of large vessels. Such an accident is speedily fatal from pulmonary embolism, the globule of air acting as an embolus. It has been suggested that under conditions of increased external pressure, *e.g.* in diving, and in the “caisson disease,” air may be liberated in the blood and be the cause of the spinal paralysis that is liable to be induced; but a more rational explanation of the mode of production of the lesion is that which refers it to the direct influence of the heightened pressure on the spinal cord (see vol. i. p. 18).

PARASITES OF THE BLOOD.—The various living organisms which have been met with in the blood have already been described. Such are the numerous bacteria which have been identified in specific diseases, and there is little doubt but that in course of time analogous organisms will be found in those affections which have infective characters, but in which at present the microbe has not yet been isolated. Now, although these diseases exhibit symptoms which denote a general infection, and although the specific microbes have been mostly found in the blood, there is but little evidence that they live there in the manner of parasites. It is true that they undoubtedly multiply in the blood, some of them to such an extent as to mechanically obstruct capillary vessels (*e.g.* anthrax), and it is also true that the products of their metabolism (toxins) exert a toxic effect upon the organism; but it has not been shown that they live at the expense of the blood itself. Indeed, it rather

appears as if the living elements of the blood were inimical to their presence, and that the microbes may be destroyed by phagocytes which seek, as it were, to protect the organism from the invaders.

It is otherwise with one well-marked group of infective diseases—the malarial fevers. Here there is now no question that the efficient cause of the fever is the entrance into the blood of a protozoal organism which is a true parasite on the red corpuscles, at whose expense it grows and develops, its morphological stages being concurrent with the stages of the febrile paroxysm, and its destructive effects being evidenced in the anæmia that ensues, and the pigmentary deposits that result from the disintegrated corpuscles. These are emphatically diseases of the blood, caused by parasites which live at the expense of the corpuscles, a position which no other of the specific infective diseases can be said to occupy.

Other hæmatozoa, of more or less transient occurrence—*en route*, as it were, for their final destination—are the several species of filariæ (p. 24), the trichina spiralis (p. 38), and the bilharzia hæmatobia (p. 5).

Lastly, certain intestinal worms distinctly influence the composition of the blood, either directly, by causing continual hæmorrhage, such as the ankylostoma duodenale, the effect of which is to induce a progressive anæmia hardly to be distinguished from pernicious anæmia (ankylostomiasis, see p. 37), or indirectly, as the various forms of tapeworm, which may bring about impoverishment of blood by withdrawal of nutriment or perhaps by toxic action, the bothriocephalus latus being specially noticeable for the state of anæmia induced by its presence.

THE MORBID CHANGES IN THE BLOOD AND BLOOD-FORMING ORGANS

The class of diseases now under consideration does not afford much material for study to the morbid anatomist; and, in respect to the alterations which the blood undergoes in its morphological elements, there is little to be added to the concise statement of facts which the reader will already have perused in the introductory article on the normal blood. Nevertheless, for the sake of uniformity of plan as well as completeness in the description of these diseases, it may be well to collate here what is known concerning the visible alterations in the corpuscles that occur in them, some of which are so characteristic as to be of diagnostic importance, and others not without some prognostic value. It will further be

necessary to describe those changes in the organs of the body that accompany the blood state, premising that these are not very extensive, and taking care to discriminate lesions which are manifestly sequential to the blood condition, although they may arise in the course of the malady. In the present state of knowledge it is not always possible to make this distinction, but, as a matter of fact, the only organs, lesions of which can reasonably be said to form a part of a blood disease, are those which are known to be related to the processes of blood formation and destruction, such as the bone marrow, the spleen and the lymphoid tissues. If other organs or tissues are found at post-mortem examinations to be also diseased, they are either involved in consequence of the blood affection, or, as it were, accidentally, and as complications which may occasionally arise in its course.

CHANGES IN THE RED CORPUSCLES.—It may be recalled that the chief departures from the normal exhibited by the red corpuscles, apart from variations in number, are to be found in respect to their (*a*) size, (*b*) nucleation, and (*c*) granular degeneration, as evidenced by their reaction to basic dyes, and the circumstances under which such changes occur are invariably those of more or less profound anæmia. The type of these changes depends to a certain extent upon the existence, in a preponderant degree, of hæmolysis on the one hand and hæmogenesis on the other. Thus the presence of a large number of nucleated corpuscles, normoblasts, is to be regarded as evidence of regenerative change, such as occurs after a profuse hæmorrhage, for such bodies exist in the adult bone marrow and in great numbers after blood loss. On the other hand the megaloblast, which occurs in the foetal but not in the adult marrow, is only present in the blood in very severe forms of anæmia, when it may be regarded as a reversion to the foetal condition and, as such, as indicating an attempt at repair; it is especially present in the blood of pernicious anæmia. It is in this disease too that most variation in the size and shape of the red corpuscles occurs, megalocytes, microcytes, and poikilocytes abounding, so that one infers that changes of this nature are regressive rather than regenerative. The granular degeneration (polychromatophil) above mentioned has also been found in this and other forms of anæmia as well as in leukæmia.

In *chlorosis*, where, as stated, the individual corpuscles, being deficient in hæmoglobin, are paler than natural, there are no very distinctive anatomical (or rather morphological) changes. The corpuscles may clump into rouleaux, and there may be an undue pro-

portion of microcytes ("microcythæmia" of Vanlair and Masius), and occasionally a few poikilocytes. Granular degeneration has been observed, but is certainly not a constant feature, whilst opinions differ as to the occurrence or not of normoblasts, some writers maintaining that they are habitually present, others that they are never to be found. The probability is that the extent to which such evidences of regeneration are met with depends upon the intensity of the disease, and especially on the degree to which the number of corpuscles has fallen.

It is, however, in *pernicious anæmia* that the most marked changes occur in the red corpuscles, and this with a constancy and to such an extent as to enable the diagnosis to be materially strengthened by microscopical examination of the blood. For there is not only a great and increasing diminution in the number of these elements, as well as a tendency to clump in irregular masses and to form rouleaux, but there is invariably great diversity in size and shape, the condition of poikilocytosis attaining, in this affection, its most characteristic features. Megalocytes and microcytes are always present; and so too are the degenerative forms which readily take the methylene-blue stain. The evidences of regeneration are, however, less prominent in this disease than those of degeneration, for although nucleated red cells may and do occur, they are rather of the nature of megaloblasts than of normoblasts, and it has been pointed out that a relatively high proportion of the former is associated with other indications of a severe and rapidly fatal attack, whilst where the latter are "numerous" and the former "few," the blood is less abnormal in other respects, and the attack of less grave prognosis.

As regards the other diseases of the "anæmic group"—viz. *leukæmia*, *splenic anæmia*, and *Hodgkin's disease*—there are no notable changes to be observed in the morphology of the red corpuscles, the main departure from the normal being their diminution in number. There is, however, one marked exception to this, and that is in the splenic or spleno-medullary form of *leukæmia*, where the blood always contains some nucleated red cells of the normoblastic type.

The blood in the *hæmorrhagic diseases* does not exhibit any marked peculiarities as regards the corpuscles. There is, as may be expected, a great decrease in red corpuscles, as in all cases of hæmorrhage—a diminution which is said to be extreme in cases of infantile scurvy; and as in post-hæmorrhagic anæmia, so also in these affections, the evidence of regenerative effort is shown in leucocytosis, and the presence of nucleated red cells (normoblasts).

The blood has been frequently examined in cases of hæmoglobinuria, and, apart from the faint staining of the plasma due to the escaped hæmoglobin, appearances have been described which suggest the fragmentation of the corpuscles or of corpuscles from which the hæmoglobin has been liberated ("shadow corpuscles"). Such elements are especially visible during the paroxysms of paroxysmal hæmoglobinuria, and have been seen in the blood taken from the finger which has been immersed in ice-cold water.

CHANGES IN THE LEUCOCYTES.—The several varieties of leucocytes, the characters of which have been described, although by no means constant in number, in physiological conditions, either relatively to each other or absolutely in respect to the total number contained in a given quantity of blood, do nevertheless occur in disease in such abnormal proportions as to constitute a truly pathological condition. Take, for instance, the two main varieties—the ordinary polynuclear neutrophil leucocyte, which in health may constitute 70 per cent of the total, and the mononuclear hyaline forms, small and large lymphocytes, which together account for about 24 per cent; it is remarkable in how many conditions these proportions may be varied, since, according to Cabot, a relative increase of the lymphocytes occurs (1) in the healthy infant; (2) in rickets, hereditary syphilis and scurvy; (3) in the adult in some forms of debility, chlorosis, pernicious anæmia, syphilitic anæmia, in the later weeks of an attack of typhoid fever, and in lactation; (4) in certain cases of Graves' disease; (5) in hæmophilia, goitre, some cases of cervical adenitis, and in tumours of the spleen; (6) during the administration of thyroid extract; (7) at the end of an attack of scarlet fever, in cases of delayed resolution of pneumonia, in measles, phthisis, and non-suppurative smallpox. This excess of lymphocytes, or lymphocytosis, as it has been termed, is not necessarily accompanied by any actual leucocytosis, but seems to imply that in these conditions, some of which it will be noted come under the head of blood diseases, there is an increase of the small mononuclear cells at the expense of the more mature polynuclear corpuscles. Indeed, in respect to the anæmic group of diseases, it may be said that, apart from variations in proportionate distribution, which may be but slight and even inconstant, the leucocytes do not exhibit such departures from the normal as would warrant the use of the term pathological in any disease except that known as leukæmia. In this affection there is not only a true pathological leucocytosis, but a leucocytosis based almost entirely on the preponderance of a particular kind of cell in each of the two main varieties of the disease.

TABLE ILLUSTRATING BLOOD CHANGES IN THE ANEMIAS.

	RED CORPUSCLES.										HAEMO- GLOBIN.		WHITE CORPUSCLES.						
	Average number per cub. mm.	Percentage of normal.	Megalo- cytes.	Micro- cytes.	Poikilo- cytes.	Poly-chromatophil degeneration.	Normoblasts.	Megablasts.	Percentage of normal.	Colour-index.	Average number per cub. mm.	Ratio to Red Corpuscles.	Polymorphonuclear Leucocytes.	Lymphocytes small.	25%	Lymphocytes large.	Myelocytes.	Eosinophils.	
Normal (adult) .	5,000,000	100							100	1.0	8,500	1 : 588	70%	25%	2.5%	0	2.5%		
Chlorosis .	3,500,000	70		+	+	+	+	0	50	0.7	8,500	1 : 400	+	+	+	+	0	0	
Pericious Anæmia	1,500,000	30		+	+	+	+	+	50	1.6	4,000	1 : 250	+	+	+	+	0	0	
Leukæmia—																			
Myelæmia .	3,000,000	60		—	—	—	—	—	60	1.0	500,000	1 : 6	—	—	—	—	—	—	
Lymphæmia .	2,500,000	50		—	—	—	—	—	50	1.0	125,000	1 : 20	—	—	—	—	—	—	
Splenic Anæmia .	3,000,000	60		?	?	?	?	?	30	0.5	6,000	1 : 500	+	+	+	+	+	+	
Hodgkin's Disease	3,000,000	60		—	—	—	—	—	50	0.8	75,000	1 : 400	+	—	—	—	—	—	
Secondary Anæmia—																			
Post Hæmorrhagic .	2,500,000	50	—	+	+	—	+	—	50	1.0	25,000	1 : 100	+	—	—	—	—	—	
Malignant Disease .	4,000,000	80							80	1.0	12,000	1 : 300	+	—	—	—	—	—	

NOTE.—This table is of course only *approximately accurate*, the variations in the blood composition amongst cases of the same disease, and in the same case at different periods, being far too great to admit of any generalisation. The main purpose of the table is to offer some means of comparison between what may fairly be considered to be the *average conditions* met with in the diseases named. The sign + indicates marked prevalence, and the sign — scantiness of the respective elements.

Thus in the ordinary form—spleno-myelogenous leukæmia—the large mass of leucocytes is composed of a form which does not exist in the circulation in normal conditions, although it does occur in the marrow. This is the myelocyte, the largest known form of white corpuscle, the characters of which are well defined and characteristic; and so constant an element is it that its presence may be deemed to be pathognomonic, warranting the use of the term “myelæmia” to this variety of leukæmia. The other form of leukæmia, the lymphatic, does not present this character of blood at all, but on the contrary its leucocytosis is mainly due to an absolute increase in the lymphocytes, which again is so distinctive that it might be termed “lymphæmia.” At one time the eosinophil corpuscles were considered to be peculiar to leukæmic blood, but the condition of eosinophilia is now admitted to be by no means limited to any special disease. In this disease also the blood furnishes minute octahedral crystals, called after Charcot, who discovered them.

In many affections there is not merely an absence of leucocytosis, but an actual deficiency in the number of white corpuscles, which average in health about 8000 per cub. mm. To this state of sparsity the term “leucopenia” has been applied. It is considered by many writers to prevail in cases of pernicious anæmia, but at the same time there may be a relative increase in the proportion of lymphocytes with occasionally some myelocytes.

CHANGES IN THE BONE MARROW.—When pathological investigation was being pursued with the intent to ascertain the true nature of the disease termed by Addison “*idiopathic anæmia*,” owing to the absence in organs and tissues of any changes adequate to its production, attention came to be directed to the bone marrow, the functions of which as a blood-forming organ were then being recognised. It was found that in many cases of this disease very striking changes were manifest, especially in the long bones and sternum. The marrow, which in the adult is of a yellowish colour from the large admixture of fat cells with the more important elements, was found to present a reddish or purplish tint, and microscopical examination proved this to be due to a great predominance of nucleated coloured corpuscles, both varieties (normoblasts and megaloblasts), cells enclosing red corpuscles, as well as the pale lymphoid cells and myelocytes. The change, which much resembles the characters met with in foetal marrow, is proved not to be restricted to pernicious anæmia in the adult, but to occur in other states of profound anæmia—as in malignant disease, or even as the result of severe and repeated hæmorrhages. Hence doubt has been

cast upon the conclusion first arrived at, namely, that this medullary lesion was an essential factor in the production of the anæmia, and a more probable view taken, that it evinces the attempt on the part of the chief blood-forming organ to repair the corpuscular loss which is the essence of the disease. In *leukæmia* also very pronounced changes are to be seen in this tissue, which takes on a pale puriform character, being sometimes quite diffuent, or else studded with minute areas of congestion and hæmorrhage. Here the normal fat cells are mainly replaced by infiltration of leucocytes, and of large nucleated myelocytes, as well as by an increase of the nucleated red corpuscles in the red-stained areas, and the products of corpuscular disintegration. The marrow cells exhibit evidences of active division, and it is probable that here is to be found the main source of the "myelæmic" condition of blood which characterises the common variety of leukæmia; for although "lymphocytes" abound in the marrow, as elsewhere in the lymphatic variety, their origin is more likely to be in the lymphoid tissues generally than in the marrow.

CHANGES IN THE SPLEEN.—These are most striking in *leukæmia*, *splenic anæmia*, and *Hodgkin's disease*, in all of which the organ is enlarged, attaining in the first-named enormous proportions. Indeed the clinical differentiation of these affections is mainly based upon the combination of splenic enlargement with and without leucocytosis, and enlargement of lymphatic glands.

In spleno-medullary *leukæmia* the spleen may come to occupy nearly one-half of the abdominal cavity; its enlargement is nearly uniform, and may almost be considered as an example of simple hyperplasia. Its capsule is thickened, and may be adherent in places to the subjacent parietal peritoneum of the diaphragm or abdominal wall. The organ is mostly firm in texture from thickening of its trabecular tissue, and is often the seat of wedge-shaped infarctions and areas of hæmorrhage. The Malpighian bodies are not unduly evident to the naked eye, but the cellular pulp is markedly hypertrophied, showing leucocytes massed together in great abundance. In lymphatic leukæmia the organ is not so much enlarged, and in the acute cases is soft and pale; the leucocytes with which it abounds are of the small lymphoid variety. Charcot crystals have been found in the spleen as well as in the blood and marrow in this disease.

The spleen in so-called "*splenic anæmia*" may also attain considerable dimensions; but although, as regards its external characters and the presence of hæmorrhages, etc., it may resemble the leukæmic organ, it differs markedly in its histological characters, which

are those mainly of a considerable overgrowth of the trabecular tissues without any increase of the pulp, but on the contrary a diminution in this element and a state of fibrous atrophy of the Malpighian corpuscles.

In *Hodgkin's disease* the spleen, although often enlarged, does not attain the dimensions met with in the preceding affections. Its appearance is quite characteristic—for it is studded with whitish masses, not inaptly compared with lumps of suet, of lymphoid tissue, sometimes to such an extent as to give the cut surface a most variegated appearance.

No special changes have been noted in this organ in either chlorosis or pernicious anæmia.

The LYMPHATIC GLANDS are affected with a hyperplastic process in *leukæmia* (lymphatic) and in *Hodgkin's disease*, and the morbid change in them is closely similar, if not identical. There are two main types of change. In the one the glands, superficial and deep, become progressively enlarged, but remain isolated from one another, enclosed in their capsules, and have a firm substance and yellowish-white colour on section. They do not caseate, and appear to be hypertrophied both as regards their cellular elements and their trabeculæ. In the other variety there is evidence of more active growth. The enlarged glands are softer, and may here and there become fused together by cellular infiltration, a condition not to be distinguished from lymphosarcoma. In many cases of Hodgkin's disease this hyperplasia is not confined to these glands, but may involve lymphoid tissues elsewhere, *e.g.* in the gastro-intestinal submucosa.

CHANGES IN OTHER ORGANS.—There are certain morbid appearances, which in a varying degree are common to all diseases of the blood. One of these is of course the condition of anæmia or bloodlessness, which is exhibited by the viscera most markedly in pernicious anæmia and the severe hæmorrhagic diseases—hæmophilia, malignant purpura, and scurvy. This *pallor* may be very striking, the vessels seeming to be empty of blood, although they really contain a pale fluid or thin pale clots. The brain shows this pallor with extreme intensity in pernicious anæmia, there being also generally associated with it shrinking of the convolutions and œdema of the membranes, such as is found in wasting diseases. Again, most fatal cases have petechial hæmorrhages, subcutaneous, subserous, or in the parenchyma of organs as well as in the retina, which are secondary to the anæmic state; whilst they abound and in many parts have the character of extensive extravasations in the

hæmorrhagic group of blood diseases. There is hardly a region of the body that is exempt from these large effusions of blood, but there are differences in respect to their site in the various affections. In malignant purpura, besides involving large areas of skin, such extravasations are met with beneath mucous membranes, respiratory and gastro-intestinal, often making their way to the surface; whilst the substance of the solid organs may be also the seat of similar hæmorrhages. There may be blood-stained serous effusion in the pleuro-pericardial and peritoneal sacs. In scurvy similar extravasations occur, but here the intermuscular planes, especially of the lower limbs and around the joints, are common seats for the spontaneous hæmorrhage; whilst in the infantile form subperiosteal hæmorrhages, near the epiphyses of the long bones, or in the orbits, are characteristic.

A pathological condition that is intimately linked with the anæmic state, and therefore to be found in almost every one of the diseases under review, is *fatty degeneration* of the muscles and solid viscera. It is a direct consequence of the lack of oxygen supply to the tissues, and has been induced experimentally by repeated blood loss. The heart is always thus affected, whilst the voluntary muscles may be merely flabby but not actually degenerate. This difference has been explained on the ground of the heart muscle being constantly in rhythmical action, calling for continual fresh supplies of oxygen, the lack of which induces the failure of nutrition that results in fatty metamorphosis of the muscle. A similar change is met with in the diaphragm, and for the same reason. Accordingly the heart presents a very characteristic appearance, being flabby and friable in texture, of brownish colour, the walls presenting yellowish specks, patches, and striæ when the degeneration is most advanced, giving to the papillary muscles the "tabby-cat striation" that is seen nowhere to such a degree as in this disease. Microscopically the muscle fibres are found to be in all stages of degeneration, from the early change of minute granules around the nuclei, to the entire replacement of the muscle substance by oil globules and granules of all sizes. There is also fatty degeneration of the lining membrane of the arteries in all these diseases. Other organs suffer this degeneration to a similar extent—such as the liver, pancreas, kidneys, and the gastric and intestinal glands—and it is again in pernicious anæmia that the most extreme conditions arise. So marked is this the case in the stomach as to have raised a question whether the lesion in that organ is really more than an effect of the anæmia, but rather a contributory or even a leading factor in the production of

the disease. There is reason to believe that this may be the case. Still in all fatal cases of the anæmic and hæmorrhagic diseases some degree of fatty change is found in most of the organs of the body.

Besides such changes, which are more or less common to this whole class of disease, there are others which are practically confined to one or other members of the group. Thus in chlorosis—which is so rarely fatal that opportunities for investigation of its morbid anatomy are rare—there has been found a condition of hypoplasia of the heart and large arteries; so that the heart is small, and the aorta no larger than the little finger; whilst associated with this occasionally is a similar hypoplastic condition of the ovaries and uterus that may be almost infantile in character. It is impossible to believe that these anatomical conditions can be common to chlorotics in general; but there is no doubt of the truth of these observations which, originally made by Rokitansky, were confirmed and extended by Virchow and other eminent pathologists. Mention may be made here of the proclivity in chlorosis to gastric ulcer and to thrombosis. The latter is most common in the saphenous and femoral veins, especially of the left side; but it also sometimes occurs in the cerebral sinuses. This tendency to thrombosis seems to be peculiar to chlorosis amongst the diseases under review.

In pernicious anæmia there is to be found deposited in the liver, spleen, pancreas, and kidneys—but especially in the first-named—much *pigment*, which, from its reaction to sulphide of ammonium, and to ferrocyanide of potassium and hydrochloric acid, is shown to be free iron. Its discovery by Quincke was an important step towards the acceptance of the hæmolytic theory of this disease. In this affection there is also apt to arise marked organic changes in the spinal cord. These changes are of the nature of sclerosis, which may not be limited to definite tracts, as in tabes or lateral sclerosis, but involve more than one region of the cord. The variability in distribution and extent of the lesions accounts for the differences in the symptomatology which may be presented. The origin of the cord degeneration is problematical. It has been ascribed to a toxic state of the blood and also to scattered hæmorrhagic foci, which are known to occur in the nerve centres as elsewhere in pernicious anæmia.

In lymphatic leukæmia, as in Hodgkin's disease, there may be nodules and infiltrations of lymphoid tissue in many organs of the body; whilst in the spleno-myelogenous leukæmia there is often

very considerable enlargement of the liver, due to a similar growth around the blood-vessels, which was once thought to be of the nature of a leucocytic or leukæmic infiltration.

There are few other important lesions which can be regarded as especially linked with diseases of the blood; but it must not be forgotten that in these, as in other general conditions of the body, complications may arise from inflammatory changes in tissues or organs. Thus broncho-pneumonia, lobular pneumonia, pulmonary œdema, pleurisy, pericarditis, and endocarditis have occurred in several instances in almost all of these affections, but they can only be considered as conditions having no direct relation with the disease which they complicate, and of accidental development.

CLINICAL CHARACTERS AND TREATMENT

A. THE ANÆMIC GROUP

CHLOROSIS—PERNICIOUS ANÆMIA—LEUKÆMIA—SPLENIC
ANÆMIA—HODGKIN'S DISEASE

CHLOROSIS

The most common form of primary anæmia, that which indeed may be taken as the type of all such affections, is the disease termed "chlorosis." It owes its name to the slight greenish tint of complexion that is often seen, especially in brunette subjects, in those who suffer from it. It is almost, if not entirely, confined to the female sex, mostly arising in the period of life between puberty and early womanhood. Cases, however, are occasionally met with in children, whilst again it has been known to first occur in mature age. At the same time most of the cases occurring late may be in those who have suffered in earlier life, for chlorosis is an affection which is very liable to recur. There is also in many an undoubted family tendency to the affection, but it cannot be said to rank usually amongst inherited diseases, and it is hardly congenital in the accepted sense, although the doctrine of Virchow upon its pathogeny entails the acceptance of a primary developmental defect in the vascular system to account for its appearance. Although there is doubtless some innate tendency to the development of chlorosis, there is also in most cases some determining condition peculiar to the individual that precedes its appearance. The conditions are those which would suffice by themselves to induce anæmia, such as lack of pure air, unwholesome diet, deficient sunlight, physical fatigue, nervous

shock or exhaustion, and such operating at a time of life when new and fresh demands are being made upon the organism might be thought to sufficiently account for its development. On the other hand, the disproportion between those exposed to such unhealthy influences and those who become chlorotic compels to the conclusion of the existence of a more essential underlying factor peculiar to the individual sufferer which is at the root of the malady. It has been already said that chlorosis is peculiar to the female sex, but cases have been recorded of "male chlorosis," although so few and far between as to suggest a doubt as to their essentially similar nature.

One characteristic of the affection wherein it differs from almost all the forms of slowly progressive and secondary anæmia is the maintenance in its subjects of a fair amount of bodily nutrition. Indeed, in not a few there is even a tendency to obesity, or at least *embonpoint*. It is insidious in onset and gradual in development in all but those rare cases where a more or less profound anæmia rapidly supervenes upon some nervous shock or strong emotion. The signs of developing chlorosis are increasing pallor, lassitude, and shortness of breath, the last-named being evoked on slight exertion from the increased strain upon the heart caused by mounting stairs, carrying weights, or rapid walking. Nevertheless it will be seen that the chlorotic is at times capable of no little energy without apparent distress, but these efforts are transient, and are speedily followed by reaction. In its fully-developed stage chlorosis presents to a marked degree all the external characteristics of anæmia. The skin generally is very pale, whitish or greenish-white in tint, often with some degree of pigmentation around the flexures of the joints; but the cheeks, especially in blonde subjects, may preserve a central rosy blush, contrasting with the surrounding *pallor*, and intensified very readily under emotion or excitement. In such circumstances the chlorotic may seem to have the hues of robust health, but closer scrutiny reveals the real condition, as denoted in the bloodless lips, gums and tongue, ears, and matrices of the finger-nails, or the pearly sclerotics and pale conjunctivæ, which give a characteristic brilliancy to the eyes.

The blood.—An examination of the blood confirms the existence of anæmia, suggested by the appearance of the skin, which, it may be remarked, is not by itself to be taken as pathognomonic. For pallor of skin may exist apart from any marked deficiency in the colouring matter of the blood, and may be consistent with health, being habitual to some persons, depending upon the condi-

tion of the skin and the cutaneous circulation. In chlorosis the drop of blood has a pale pinkish colour, and seems to be more fluid than natural. The red corpuscles form rouleaux, but not so readily as in health, and individually exhibit considerable variation in size, without, however, showing such striking anomalies in shape as is the rule in pernicious anæmia. The comparative pallor of each corpuscle can often be appreciated, and it accords with the invariably low amount of hæmoglobin which, as previously noted, seems to be out of all proportion to the deficiency in number of corpuscles. The blood count alone is not therefore an index of the intensity of the anæmia. As a rule in chlorosis the numbers are higher than might be anticipated, so that if in any case of this disease the numbers fall so as in their percentage to approximate closely to the loss of hæmoglobin, the coexistence of some additional anæmiating influence may be suspected. It is, of course, probable that such an influence may always be present to a certain degree, for the chlorotic is quite as liable to be exposed to it as is the healthy; but the condition, which is above all characteristic of chlorotic blood, is, that it is marked by an insufficiency of hæmoglobin rather than a deficiency of the hæmoglobin-carriers. The other characters of the blood are thus concisely summed up by Cabot:—

“1. Blood as a whole: very pale in marked cases, very fluid, but coagulates rapidly. Fibrin not increased. Specific gravity usually low, running parallel with the hæmoglobin. 2. Red cells: average 4,000,000 when patient is first seen; very rarely go below 1,000,000. The majority of them are small-sized, pale, often deformed. Nucleated corpuscles are rare (normoblasts as a rule). 3. White cells not increased. Lymphocytosis; occasionally eosinophilia. 4. Blood-plates increased.” (*Clin. Exam. of the Blood*, p. 139.)

General nutrition and physique.—It was remarked above that the subjects of chlorosis do not appear to suffer in general nutrition, being mostly well developed or having the appearance of good development. It may be that the blood state itself is responsible for the tendency to accumulation of fat that so many of them exhibit, whilst the musculature is proportionately poorly developed. There is not only disinclination to exertion, but often a physical inability for it, and muscles which have primarily suffered from lack of oxygen are still further disabled from action by the effects of enforced disuse. This may account for the lassitude and “tired feeling” so many experience, which, however, may pass off as the day wears on, not because the muscles really regain their vigour,

but from the operation of nervous stimulation in a subject whose nervous system is readily excited. It is a well-known fact that the subject of chlorosis, who is mostly a heavy sleeper, awakens unrefreshed, finds it difficult to rise, and experiences much lassitude throughout the day, does nevertheless considerably brighten up towards nightfall, and becomes more wakeful and energetic than her companions. Many a chlorotic is the life of the ball-room, but she pays the penalty of drawing so largely on her nerve power. It would seem as if she were enabled by mere excess of nervous energy to overcome the neurasthenia which one might expect to have been a constant concomitant of her anæmia, but the result of this draft upon her nervous reserves is felt the following day in the inevitable reaction to lassitude and weakness. The distaste for exertion is also increased by the fact of its being accompanied by one of the most constant of the subjective symptoms of chlorosis, namely, shortness of breath. For, although under the spur of mental excitement she may undergo considerable muscular exertion, there is no mistaking the fact that this demands from her more respiratory effort than is seen in the healthy. And, as said, this dyspnœa may be evoked by any slight departure from the amount of ordinary muscular effort. It may not appear when walking on the level, but she cannot run a few yards without panting for breath and getting a "stitch in the side," whilst the mounting of stairs or the carrying of weights becomes more and more difficult and irksome from the same reasons. Indeed this dyspnœa may be the first symptom of her failing health that the patient herself notices, and although she may struggle against it she has eventually to yield. At the same time she may be liable to suffer from palpitation. The dyspnœa is probably due to two conditions: first and foremost is the state of anæmia, and second is the cardiac debility which that anæmia induces. The muscles, in order to respond adequately to the increased effort demanded of them, require more oxygen, and the quickening of the circulation that results calls for a like effort of respiration, and this is felt as dyspnœa. But if the heart does by its acceleration endeavour to bring more blood to the muscles, it is also itself enfeebled, since it too requires an adequate oxygenation for its muscular work, and so by a vicious circle the call for oxygen becomes more urgent and the impoverished blood less able to furnish it. Thus a limit to its renewal is reached when the subjective sense of dyspnœa becomes so imperative that there is nothing for it but to abandon the struggle and seek the rest which nature demands.

Circulatory symptoms.—Prominent amongst the signs of chlorosis are those yielded by the cardio-vascular system. The *pulse* may be full and even of high tension, at least in the early stages of the disease, although with advancing anæmia and cardiac weakness it becomes softer and quicker; and its rate is accelerated unduly in the change from the recumbent to the sitting or standing posture. The *heart's apex beat* may be felt somewhat lower and more external than natural, whilst on percussion the *area of dulness* is increased. These signs probably indicate some degree of dilatation of the heart, although they are equally explicable on the ground of retraction of an imperfectly expanded lung. The so-called "*hæmic murmurs*" are always present, sometimes in great intensity and number. The most common precordial bruit is a systolic blowing murmur, having its maximum intensity at the pulmonary cartilage; but a systolic murmur of much the same quality may be heard in the mitral area, and to the right of the sternum over the aortic cartilage. Much controversy has arisen as to the mechanism of production of these bruits. The apical murmur is doubtless really one of mitral regurgitation, caused not by any defect in the structure of the valve but by inadequate closure from enfeeblement of its papillary muscles as well as by the dilatation of the ventricular cavity and consequent stretching of the mitral orifice. The arterial bruits cannot be similarly explained, although the theory that the most constant murmur audible over the pulmonary area is really due to mitral regurgitation rendered audible at this spot by conduction through the enlarged auricle that here overlies the pulmonary artery has been strongly advanced. In seeking for an explanation of these basic bruits it is to be remembered that they are met with in other forms of anæmia besides chlorosis, that in anæmic states very slight pressure will evoke similar bruits over arterial trunks, and that most characteristic of all is the hum that can be heard over the jugular vein at the root of the neck. This murmur can be recognised by its continuous character, rising and falling with respiration, louder in the upright position and during inspiration when the venous flow is most marked. Its character has led to its being termed the "humming-top murmur" or "bruit de diable." It is generally better heard over the right jugular than the left, and its loudness seems to bear some relation to the intensity of the anæmia; and when best marked it can be "felt" as a continuous thrill by the fingers placed lightly over the vessel. Nor is it the only venous bruit that can be heard in anæmic subjects, for competent authorities declare that a similar sound is audible over

the site of the torcular Herophili. These venous bruits as well as the pulmonary and the less common aortic murmurs bear a definite relation to the state of the blood, for they diminish in intensity and disappear as the quality of the blood improves. Yet it is difficult to explain their occurrence unless on the theory that the quantity of blood is diminished as well as its quality altered. There is no physical reason why change in quality of the circulating fluid should produce a bruit in these channels, but there is an acoustical reason for their production if the volume of blood be insufficient to adequately fill the vessels at parts of the channel which are so conditioned as to be unable to adapt themselves to lessening of their contents. The problem can hardly be considered as completely solved, since the explanation that seems most feasible involves a postulate which is difficult of admission, and is moreover at variance with the doctrine that the mass of blood is by no means decreased in this disease.

Œdema.—The condition of the blood in the chlorotic is responsible for a symptom that is often complained of but is not very significant, namely, dropsical swelling of the feet and ankles. It is purely a mechanical dropsy and seldom attains any marked degree, being at its worst at the close of the day and disappearing during the night's rest. As a rule it amounts to little more than puffiness around the malleoli and some pitting on pressure over the dorsum of the foot. There would seem to be also an undue tendency to *thrombosis*, so that an œdema limited to one extremity should lead to careful examination of the veins of the leg, for the thrombus may extend from the smaller into the larger and main veins. This is not a common event, and even rarer, but still frequent enough to suggest some special liability on the part of chlorotics, is the formidable thrombosis of the cerebral sinuses which may terminate a severe case of chlorosis. The indications of this grave complication are the supervention of severe headache followed by convulsions and coma, with a rising temperature. It is said that there is no increase of fibrin in the blood, so that the thrombosis cannot be attributed to a condition of hyperinosis. There is also in some subjects a liability to *spontaneous hæmorrhage*, such as epistaxis and menorrhagia, the supervention of which may gravely aggravate the condition and even imperil life. If hæmatemesis occur it is most likely due to gastric ulcer.

Headache of less formidable significance than that just mentioned is very common in chlorosis, and is often doubtless dependent in large measure upon constipation. It is by no means always of the

frontal variety, for occipital and vertical headaches are liable to occur. They are attributed to the anæmia itself and are often called "anæmic" headaches, and many of them are no doubt truly neuralgic, for neuralgia in other situations—*e.g.* of the fifth nerve, cervico-occipital, and intercostals—is not uncommon.

In severe cases there may be *swelling of the optic disc*, and this to such an extent as to suggest cerebral disease, especially if headache and vomiting be also present. The writer recalls one such case where grave anxiety was caused by this combination of symptoms, which was, however, dispelled as the patient regained her health and lost these signs of intracranial disorder.

On the side of the *digestive system* there are often marked abnormal symptoms. *Loss of appetite* is certainly more common than the capricious, depraved, and inordinate appetite that was regarded by older writers as one of the characteristic features of the "green sickness." *Thirst* is sometimes complained of—especially in severe cases. The *tongue* presents, as a rule, no marked change beyond striking pallor, and it may be some flabbiness and pitting from the teeth; and it is usually fairly clean. Occasionally where constipation is marked, it is coated and the breath is foul. There is often some *epigastric pain* and discomfort after taking food; but, on the other hand, cases occur of true gastralgia, in which the pain is actually relieved by food. There would seem to be a proneness to the development of gastric ulcer, which may form a very serious complication. *Constipation* is marked in many cases, but is not an invariable symptom.

The *urine* is fairly copious, pale, and of low specific gravity, presenting no material abnormality in uncomplicated cases.

Amenorrhœa is an early and common symptom, and even if not absolute there may yet be marked deficiency in the menstrual function, which is mostly to be regarded as the result of the anæmia. In some cases, however, the uterine organs are imperfectly developed.

Temperature.—Lastly, chlorosis is for the most part regarded as an apyrexial malady, but there are few well-marked cases which run their course without a certain amount of febrile disturbance. This may not be regular or continuous, but not infrequently the temperature will rise to 99° or 100° without any intercurrent inflammatory complication to account for it. The occurrence of fever in anæmia, where naturally oxidation is lessened, appears to be paradoxical, and has not as yet received any satisfactory explanation.

The *diagnosis* of chlorosis has to be made from the numerous

forms of secondary or symptomatic anæmia, and is therefore often arrived at only by exclusion of conditions liable to lead to this result. One of the most important is tuberculosis, which in an early stage may be so masked by anæmia as to fail to be detected. Careful observations of the temperature and repeated physical examination may be required before a definite opinion can be arrived at. The history of the case is mostly sufficient to exclude anæmias resulting from losses of blood. Even if sufficient facts be lacking, something is to be gained by an examination of the blood, which, after hæmorrhage, exhibits not only a marked reduction in the number of red corpuscles, with leucocytosis and evidences of regeneration in the presence of nucleated normoblasts, but does not possess the low "colour-index" so characteristic of chlorosis. Similarly there is not much difficulty in distinguishing the disease from pernicious anæmia by blood examination alone, but it is a moot question whether this latter disease may not occasionally (though rarely) be grafted upon a primary chlorosis.

Of the **complications** of chlorosis the most common are *thrombosis of the veins of the leg*, which is evidenced by white swelling, and the occurrence of *gastric ulcer*. Bearing in mind the frequency of gastric dyspepsia and also the liability to gastralgia, the determination of the presence of an ulcer may not always be an easy matter, unless vomiting and especially hæmatemesis supervene. *Inflammatory affections* such as tonsillitis, pneumonia, pleurisy, pericarditis, and nephritis occasionally arise, but that there is any undue liability to such affections in the chlorotic may be questioned. That the blood condition may render the subject more vulnerable to the causes of such diseases is of course not improbable; and the same may explain the tendency to *tuberculosis* which sometimes develops. Although, as already remarked, the anæmic state may only be the indication of the presence of tubercle and not its precursor.

The **prognosis** of chlorosis is in the majority of cases favourable, owing to the amenability of the disease to treatment; but the liability to recurrence is great, and the chlorotic may for long remain more or less of an invalid. Nevertheless it is surprising how capable for the duties of life many of these subjects are, in spite of an almost chronic state of blood poverty, whilst very many who have been profoundly chlorotic in adolescence entirely lose the tendency, and if they marry may bring up healthy children. The differences that are met with in the after-history of chlorosis suggest some integral differences in the essential nature of types of

the malady, which may some day be explained. As regards the attack itself, recovery may be much retarded by complications, especially those which involve further drain on the blood; and a fatal issue may occur from gastric or uterine hæmorrhage which would not in a previously healthy subject have brought about this termination. There is also lessened recuperative power from severe inflammatory or infective disease. The duration of an attack of chlorosis is very variable. In some cases even of severe type rest and medication may restore health within a few weeks. Some cases even get well by mere change of scene and occupation, combined with rest. Others are rebellious to the most persevering treatment.

Treatment. — Considering the circumstances under which chlorosis so often develops, it is clear that amongst the measures of treatment a first place must be taken by *prophylaxis*. The avoidance of conditions likely to impair health, such as dwelling in confined and ill-ventilated rooms, insufficient or improper diet, excessive physical or mental strain, is so obvious as not to need mention; but as in most cases the patient has already been subjected to these or similar influences, which have played no small part in the production of her malady, steps should be taken to remove her from them, not for prophylaxis but to improve her chances of recovery. Thus a potent means to this end is *rest* in the fullest sense. Many a chlorotic girl demurs to the enforcement of this rational prescription, but there can be no question that it materially aids in her restoration to health. In severe cases absolute confinement to bed is called for; and even in the earlier stages, when symptoms are less urgent, it may be well to insist on a more prolonged rest in bed than a healthy girl requires. Attention to *diet* is another point of importance, and in particular the avoidance of indulgence in tea and coffee, pastries, and other indigestible articles, for which the chlorotic sometimes exhibits an undue fondness. She should be encouraged to take meat, and made to overcome her repugnance to this, being encouraged to prefer it rather under- than over-cooked. Milk and milk-puddings, fresh vegetables and fruits are also to be recommended. With the chief meal, some red wine is undoubtedly useful. Although rest is a primary consideration, the patient, if not too severely attacked, should take regular and sufficient *exercise* in the open air, but avoid any exhaustion. This recommendation is not always easy to enforce, because of the somewhat excessive nervous energy that some chlorotics possess; but if they do thus draw on their reserves, they suffer for it afterwards. They should, however,

live as much in the open air as possible, and when circumstances permit should spend the winter months in resorts where *sunshine* can be had in great abundance; for the influence of sunshine as a hæmatinic is universally admitted. *Bathing* and tepid sponging and massage are valuable adjuncts to other measures for improving the general state of health.

As regards *medication* the chief remedy is iron. Its efficacy has long been known, and its action in chlorosis, however explained, is that of a specific. Nor should it be given in small amount, for more good is done by doses which would not be tolerated by the healthy than by small quantities, and it would seem that results are more rapidly obtained by the stronger preparations than by those in which it is given in blander form. It is most frequently prescribed as Blaud's pill, which contains sulphate of iron and carbonate of potash (of each $2\frac{1}{2}$ grains), in the belief that the more easily assimilable carbonate of iron is thus presented. But experience shows that quite as efficacious a result is obtained by giving pills containing two or three grains of the dried sulphate of iron. Others have found equally good results from the perchloride, whilst there are numberless preparations of a milder quality that may be had recourse to if these fail. There does, however, seem to be ground for the belief that the efficacy of iron in chlorosis depends not merely on the amount which is actually assimilated, but also on the local action of the metal upon the intestinal mucous membrane. Those who advocate the combination of carbonate of potassium with the sulphate of iron consider that the alkali aids in the assimilation of the latter, and some recommend a course of alkaline treatment preparatory to the ferruginous. But as in the combined form the actual salts ingested are probably sulphate of potassium and carbonate of iron, it is also surmised that the former is of utility from its slightly laxative action. Indeed the prescription of laxatives either in conjunction with or separately from the iron salt is mostly advisable and indeed often actually necessary. In this case sulphate of magnesia or aloes may be given, or a morning draught of Friedrichshall, Hunyadi Janos, or Apenta water. Sir A. Clark, who considered constipation to be a chief element in the production of chlorosis, laid great stress on the value of purgation as an accompaniment of or a precursor to the administration of hæmatinics. It is seldom that iron is not tolerated, but if this should be the case, arsenic may be substituted for it. The mineral acids, with some vegetable bitter, as calumba or gentian, are also often serviceable, hydrochloric acid being especially advocated as aiding digestion, although, it may be

remarked, the gastric juice in chlorosis is said to contain an excess of this acid, whilst in cases of marked cardiac debility the addition of strychnine or small doses of digitalis can be made.

In this and in other anæmic disorders much benefit has often been derived from the prescription of dried ox blood both by the mouth and in the form of rectal injection, which some years ago was more in favour than it is at the present day, its place being apparently taken by preparations of hæmoglobin.

PERNICIOUS ANÆMIA

The *appearance* presented by the subject of pernicious anæmia is so striking as to be almost pathognomonic. It is not the mere fact of intense anæmia, which of course may be induced in very many ways, but the state of pallor is combined with a marked faintly yellowish or lemon tint, recalling jaundice, but not of the depth of colour of true icterus, that stamps the case as exceptional. If such a type of anæmia be present in an adult without any evidence of malignant disease or history of blood loss, the probability is that the case is one of this class, and the conclusion thus arrived at will be materially strengthened if in its history and symptoms the case be found to conform more or less to the following facts.

General condition.—The anæmia has come on somewhat insidiously; *pari passu* with its development there has been on the part of the patient a growing disinclination as well as a disability to exertion, either physical or mental. He is not only easily fatigued, but he has become unnaturally listless, so that his whole character has altered. He is as conscious of this change in himself as are his associates, who further observe that these indications of debility are accompanied by a progressively increasing pallor. It often happens too that with these indications of failing health he has been troubled with gastro-intestinal derangements, to which he may ascribe his weakness—*dyspeptic symptoms*, such as attacks of vomiting, and of diarrhœa, which have arisen apart from any errors or extravagancies of diet. In some cases these digestive disorders are most pronounced, especially the diarrhœa, so much so as to suggest the presence of ulceration of the colon; and their prominence may serve to draw off attention from the real disease, to the development of which they do no doubt contribute. Meanwhile other symptoms directly referable to the progressing anæmia make their appearance. The patient may not have lost much, if any, flesh; but his *asthenia* is pronounced. His limbs seem to be flabby, and he suffers much

from *palpitation* with *shortness of breath* on any unusual exertion. Some *œdema* may appear about the ankles, and he is forced to abandon his vocation and lie up.

Examination shows that the *pulse* is rapid, small and of low tension; the *action of the heart* feeble; the impulse diffuse and fluttering. A systolic bruit is to be heard over the præcordia both at the pulmonary cartilage and at the apex, generally soft in character, but occasionally so harsh and grating as to simulate an exocardial rub. In the neck will be heard a loud *jugular hum*.

From time to time there will be *febrile attacks*, the temperature rising to 102° or 103° , but the pyrexia runs an irregular course, and in a well-marked case the elevation may be long continued.

There is also a *tendency to hæmorrhage*—attacks of epistaxis, perhaps of hæmatemesis, melæna, or metrorrhagia—but large bleedings are not frequent. The writer has, however, seen a case which terminated fatally from cerebral hæmorrhage. On the other hand a very constant sign, if the anæmia has become pronounced, is the presence of retinal hæmorrhages, which can be seen by the ophthalmoscope to be scattered about the periphery of the retina, with or without any neuro-retinitis.

An examination of *the blood* which flows with difficulty from the puncture reveals conditions that are wellnigh distinctive. Reference has previously been made to these; but, as in the case of chlorosis, one cannot do better than quote the summary of these changes given by Cabot as follows:—

“1. Red cells about 1,000,000 per cubic millimetre; 2. White cells much diminished; 3. Hæmoglobin variable, sometimes increased relatively (= high colour-index); 4. Deformities in size and shape of red cells in many cases; 5. Increase in average diameter of red cells; 6. Polychromatophilic red cells; 7. Megaloblasts more numerous than normoblasts; 8. Lymphocytosis; 9. Small percentage of myelocytes.”

These characters are almost sufficient to distinguish the case from one of anæmia due to organic disease, *e.g.* latent cancer of the stomach; but it is questionable whether they are absolutely distinctive, for where a progressive anæmia caused by repeated hæmorrhages is present, the characters are much the same. In such a case, however, there will probably be leucocytosis.

The *urine* sometimes, but not invariably, presents peculiarities which are considered to be of great importance as indicative of the hæmolytic nature of the malady. Thus it will be of an unnaturally high colour, from excess of pathological urobilin, and may deposit

pigment granules believed to be derived from disintegrated corpuscles. In most cases this character of the urine occurs coincidentally with paroxysms of the disease, which often runs a remittent course. There may be an excess of indican in the urine, and occasionally of uric acid.

On the side of the *nervous system*, in addition to mental disturbance—such as defects of memory, of concentration and application to subjects requiring thought—the patient may suffer from vertigo, headache, and drowsiness. Sometimes in an advanced case there will be more active disorder, such as delirium, amounting perhaps to mania. In view of the extensive sclerosis which has been described as occurring in the spinal cord, it is remarkable that so few cases present any marked spinal symptoms during life. However, disorders of sensation, muscular weakness, and an ataxic gait, with loss of knee-jerks, have occasionally been recorded.

Course and termination.—Although a progressive, and, it is to be feared, an invariably fatal affection, the course taken by pernicious anæmia is not uniformly downward. For although on an average the duration of illness does not exceed twelve or eighteen months, it often happens that there are occasional periods in which the morbid process seems to remit, and this, which is often with justice ascribed to the effects of treatment, may perhaps be part of the natural history of the affection. The period of remission varies from a few months to several years (Dr. Byrom Bramwell had a case in which the patient remained fairly well for twelve years, when he relapsed, and ultimately died), but the tendency to relapse is very great. The *mode of death*—unless accelerated by intercurrent disease, as pneumonia or cerebral hæmorrhage—is that of asthenia or gradual exhaustion, but towards the end there may be some distressing dyspnoea and anxiety. In other cases syncope from heart failure carries off the patient. The actual *duration* of the disease from the first appearance of symptoms to the fatal termination is most variable—from six months to two years might be given as an average; but there are many cases in which, as above-mentioned, long periods of apparent convalescence or remission occur, and more than one relapse may intervene before the final attack.

The *diagnosis* of pernicious anæmia from the other primary diseases of the blood is not difficult, for they each have their distinctive characters. It may, however, in young females be for a time doubtful whether the case is one of chlorotic anæmia or the graver malady. The comparative infrequency of pernicious anæmia

at that age would tell against the case being of this class, whilst an examination of the blood and the therapeutic test should practically determine the point. Cases do rarely occur which, commencing as chlorosis, seem to pass into pernicious anæmia. Chronic anæmia from small and repeated blood loss may closely simulate the pernicious form, and indeed a good example of this is to be found in "ankylostomiasis," which, prior to the discovery of the parasite, was regarded as an idiopathic anæmia (page 37). Examination of the stools may reveal the presence of the ova of this parasite, which will also materially influence the prognosis of the case. The value of anthelmintic remedies is strikingly shown when by their aid what appeared to be a fatally progressing anæmia is checked and turned on the road to recovery. The anæmia and cachexia which accompanies malignant disease, especially cancer of the stomach, may be mistaken for pernicious anæmia, the more so if, after careful examination, no overt signs of cancer be detected. Perhaps the resemblance is heightened by the fact that a condition of gastric atrophy has been found in cases of pernicious anæmia, and some, reversing what might be considered the natural order, have described cancer of the stomach as developing and complicating pernicious anæmia. The emaciation of gastric carcinoma is a point of difference from the condition seen in the primary blood disease; and according to Cabot the blood in malignant disease, although very impoverished in red corpuscles, differs from that of pernicious anæmia in containing normoblasts rather than megaloblasts, and a leucocytosis of neutrophil leucocytes rather than lymphocytes—differences which may not be sufficiently marked (except to the expert) to be allowed great diagnostic value.

As regards **prognosis**, it will have been already evident that unfortunately, as regards the ultimate issue, this disease is inevitably fatal, yet many cases remit for variable periods, the tendency to relapse being sometimes long held in abeyance. It is not unlikely that these remissions have become a more prominent feature of the disease since the introduction of arsenic as a remedy for it.

The **treatment** of pernicious anæmia is in its general principles, as to rest, hygiene, and diet, conducted on similar lines to that of chlorosis, and it is mainly in respect to drugs that divergence is marked. For in the vast majority of cases, iron, the specific for chlorosis, and valuable in many other anæmic conditions, is powerless for good in pernicious anæmia. It is quite true that there are a few cases on record in which iron has done good, but they are exceptional. There is, however, a metal which has been proved to

be of great utility, and the introduction of which in the treatment of this disease is owing to Dr. Byrom Bramwell. This is *arsenic*, a remedy of admitted value in other blood diseases. It is best given in the form of Fowler's solution (liq. arsenicalis) in doses of ℥iii. to ℥v., and may be continued for a long time. It may also be given as a pill in the form of arseniate of iron ($\frac{1}{16}$ gr.). The chief drawback to its use is its liability to cause gastric irritation, but with careful regard to dosage and to time of administration this may be overcome. Its long-continued use is likely to lead to cutaneous pigmentation (melanoderma), or even neuritis, but though it may be obviously doing good by improving the condition of the blood, its administration should under these circumstances be suspended. The corpuscular count affords the best test of the value of this or of any other remedy employed in this disease, although it is sometimes difficult to be certain whether the improvement is not due to the naturally remittent, or rather intermittent course of the malady. *Bone marrow* has been prescribed in some cases with at least temporary benefit; it can be given in the form of "tablets," or taken with the food in the raw state. *Intestinal antiseptics*, such as naphthol, or salicylic acid, have been given, especially since the views regarding the seat of the hæmolysis (in the portal blood) have come to be accepted, and good results have been recorded. The same may be said of *oxygen inhalations*, and even of *blood transfusion*, but it is impossible to accept such records of success as indicative of measures that are generally applicable, for in most, possibly all, such cases the improvement in the blood state has been transient and temporary.

LEUKÆMIA

The separation of cases of leukaemia into at least two distinct categories—originally pointed out by Virchow in 1847—is of pathological rather than clinical significance. It is based on the fact that in the one group the increase of white cells is almost wholly made up of uninucleated lymphocytes (mostly small in size), whilst in the other the larger myelocyte predominates. So striking is this difference that to the one class the term "lymphæmia" has been applied, and to the other that of "myelæmia." It has been already stated that in the lymphæmic class there occurs enlargement of the lymphatic glands suggestive of the source of origin of the predominant type of leucocyte, whereas in the myelæmic such lymphatic glandular affection is wanting. In both classes the spleen

may be enlarged, but it is in the myelæmic that this organ attains the great dimensions which give rise to the appellation "splenic leucocythæmia," as well as to the notion that the spleen was the organ which was mainly responsible for the leukæmic state of blood. Since, however, the condition of the bone marrow in this disease has been studied, pathological opinion has assigned to this organ the rôle of being the source of this variety of leukæmia, whilst the spleen has been regarded as playing a somewhat passive part. The matter can hardly be said to be finally determined, for it is difficult to believe that so enormous an enlargement of the spleen should take place unless it were in some way bound up with the blood change. Provisionally, therefore, this, the ordinary type of leukæmia, is termed "splenic-myelogenous or spleno-medullary," and it is this variety in which the blood has the myelæmic character. In the other variety—long known as "lymphatic leukæmia"—there may also be some enlargement of the spleen, but never to the extent noticed in the far more common type. It occurs too for the most part in young subjects, and the cases of "acute leukæmia" pertain to the lymphatic class. It ought to be added that, as regards the state of blood as well as of the organs involved, cases do occasionally occur which seem to fall under neither group, but to one which partakes of the characters of both.

Clinical characters.—Deferring for the present a description of the comparatively rare cases of "acute leukæmia," we may now consider the clinical features of the disease that is commonly met with. It will not be necessary to treat separately of the two pathological types, since in their clinical course they resemble each other, their differences being anatomical and hæmatological.

Leukæmia then, broadly speaking, is a chronic affection, met with at all periods of life, but most frequently in the adult between thirty and forty years of age, and more commonly in the male than in the female sex. Insidious in its onset, it often does not come under the notice of the physician until the physical discomfort of an enlarging abdomen, or of swelling of cervical glands, added to a progressive asthenia, with other indications of failing health, compel resort to medical advice. This fact shows that it is for the most part a painless affection, and it also renders it impossible to determine the date of origin of the malady, and therefore to accurately estimate its total duration.

The *earlier symptoms* are a gradual loss of physical energy and endurance, a sense of malaise, together with anorexia, and perhaps intermittent gastro-intestinal disturbance, such as irregularity of the

bowels, attacks of diarrhoea alternating with constipation. There may not for some time be any pronounced anæmia, but gradually this develops together with the concomitant symptoms of dyspnoea on exertion and muscular weakness. There is also gradual emaciation, which, as the disease advances, may become very marked. The skin assumes a dusky or tawny tint, not unlike that met with in the subjects of malaria; whilst there would appear to be undue proclivity to eczematous and pruritic affections.

A not uncommon symptom of the early period is epistaxis, and in the female menorrhagia. This *hæmorrhagic tendency* develops as the disease progresses, and, as will be seen, may give rise to disturbances of vision and hearing by its occurrence in the retina and internal ear, or to even graver results.

When for a variable period these or similar symptoms have occurred on and off at intervals, the patient (in the usual form of the disease) begins to appreciate an enlargement of the abdomen. He may with this experience a sense of weight and fulness beneath the left lower ribs. Examination readily proves the existence of an *enlarged spleen*, which by this time may reach nearly to the umbilicus and the iliac crest. There is seldom any difficulty in determining the nature of the swelling. The smoothness of its surface; its rounded anterior margin, in which the well-marked and characteristic "notch" can be felt; the continuity of the tumour below the ribs, with the splenic area of dulness behind them, itself extending upwards; and the existence of resonance in the loin, due to the subjacent colon, are points which differentiate it from a renal tumour, with which alone it might be possible to confound it. There is also often some *enlargement of the liver*; and as time goes on these two organs may come to occupy the main part of the abdomen, displacing the intestines downwards and backwards.

In some cases *tenderness over the sternum* is met with, possibly associated with the changes that are in progress in the bone marrow. In others, with no or only slightly appreciable splenic enlargement, there will be obvious *enlargement of lymphatic glands*, especially of the cervical and submaxillary chains, but also of the axillary and inguinal. Symptoms too may arise indicative of the presence of enlarging bronchial and mediastinal glands; in fact the case might be regarded as one of Hodgkin's disease (*q.v.*), were it not that the blood presents marked leukæmia. It is for this reason that Hodgkin's disease has been termed "pseudo-leukæmia."

When leukæmia has reached this stage—*i.e.* of well-marked splenic tumour or of glandular enlargements—its course is gradually one

in a downward direction. Sometimes this is interrupted by periods in which there may be no progress, the spleen may not continue to enlarge, the blood may even become more nearly normal in its relative composition, and hopes may be raised of complete recovery. It is not always possible to be certain that such *intermissions* are due to the therapeutical measures employed, for the same difficulty confronts the observer here as in the case of pernicious anæmia, namely, the old problem in all treatment of "*post*" or "*propter hoc*." If the arrest be due to treatment, there comes a time when this ceases to have any influence, and once more the disease progresses unchecked. The stationary interval may be long,—I have known it to last for two years,—but it is very doubtful if permanent recovery is ever established. On the other hand, the case may progress uninfluenced by treatment, and this, which constitutes the middle and terminal stages of the disease, is marked by the appearance of more pronounced symptoms than have hitherto arisen.

The condition of anæmia gradually becomes more evident. It may be increased by the occurrence of hæmorrhages, for besides epistaxis there may be attacks of hæmoptysis or hæmatemesis, or intestinal hæmorrhage or hæmaturia. *Ophthalmoscopic examination* may reveal streaks of hæmorrhage and whitish patches in the fundus oculi, which are sufficiently characteristic to have been denoted "leukæmic retinitis." The position of these changes may account for the fact that often vision is not deranged, whilst sometimes this is so much affected that (as in Bright's disease) the first suspicion of the true nature of the patient's malady may be that which is given by the ophthalmoscope. Similar changes may take place in the delicate structures of the internal ear, so that *tinnitus and deafness* are complained of, and vertiginous attacks suggestive of Menière's disease may be experienced.

Mention of vertigo—in most cases doubtless due to these changes in the ear—suggests the occurrence of cerebral symptoms, of which that used to be regarded as one. *Headaches* are not uncommon, and in the later stages more active disturbances, such as delirium or mania, whilst cerebral hæmorrhage may terminate life.

In respect to *circulatory and respiratory symptoms*, there are few which can be regarded as directly dependent upon the disease, except those attributable to the anæmic state. Thus, in a well-marked case, there are present the cardio-vascular signs of anæmia, cardiac, arterial, and venous bruits, a rapid and soft pulse. The heart is displaced upwards by the enlarging spleen. There is some tendency to *thrombosis*, although not to the extent that might *a priori*

be expected. However, one symptom, sometimes among the early phenomena, is painful and persistent priapism, which has been attributed, and with reason, to coagulation within the corpora cavernosa. Amongst the complications are bronchitis and broncho-pneumonia, more liable to occur in the lymphatic variety, where serious pressure effects may be produced by the enlarging mediastinal glands.

The *urine* is generally of high specific gravity, owing to a notable increase in urea and uric acid.

The progress of the disease is for the most part sub-febrile. The *temperature* may be slightly above the normal, and, at times, may be as high as 102° or 103° . Indeed, in some cases, very definite pyrexial exacerbations may occur, the type of fever being mostly irregular—at times remittent, at others intermittent. In one well-marked case, seen by the writer, there were paroxysms of intermittent fever, closely simulating malarial fever, accompanied by chills and profuse sweats. This patient had never suffered from malaria, but she had lived in a low-lying district on the south coast, where ague was not entirely unknown.

Gradually increasing asthenia; the discomfort arising from the enlarging abdomen; the weight of the splenic tumour, varied by attacks of pain in this region (probably due to peri-splenitis); failing appetite, almost to total anorexia; attacks of diarrhoea, of faintness and giddiness, and a wearying headache, mark the progress of the disease, together with steady emaciation. Towards the end, which, unless produced by cerebral hæmorrhage, may come on slowly from asthenia, with little impairment of faculties, œdema may occur in the lower limbs, with hydrothorax and ascites.

The *duration* of such a case, from the time that its nature has become manifest, may be from two to three years. What has been its total duration it is impossible to determine.

It may be convenient here to once more refer to the *characteristics of leukæmic blood*, as it is upon them that the diagnosis of the disease is founded. It has been already pointed out (pp. 291, 322) that leucocytosis is not the same thing as leukæmia. Leucocytosis may be a normal condition, transient and temporary, as during digestion, or in the infant or the pregnant woman, whilst it marks many inflammatory affections, and some chronic diseases, such as cancer. But in all these circumstances the increase of the white blood cells is almost wholly of those forms of corpuscles which occur in the normal blood; and there is never, as in leukæmia, such a vast preponderance of the mononuclear lymphatic elements as characterises lymphatic leukæmia, nor the appearance in the blood of the large

myelocytes which form the leading feature of the spleno-medullary variety. Indeed, if the term "leucocytosis" be restricted to an increase in normal constituents, it hardly ought to be applied to leukæmic blood, where the normal polymorphonuclear neutrophile is much less abundant proportionally than in health. Thus the chief leucocyte elements in normal conditions are the neutrophile multinuclear cell, constituting about 70 per cent of all the leucocytes present, and the small uninuclear lymphocytes, which form another 25 per cent. In spleno-medullary leukæmia the normal neutrophile cells seldom, if ever, exceed 50 per cent of the mass of leucocytes, and often fall much below this, whilst the myelocytes account for nearly all the remainder, there being perhaps a few scattered lymphocytes, as well as eosinophil corpuscles, some of the myelocytes being also eosinophilous. In lymphatic leukæmia more than 90 per cent of all the leucocytes present are of the lymphocyte (small and large) variety, which have been regarded as immature forms of the adult white corpuscle, here almost inconspicuous, whilst few myelocytes, if any, are present. The blood then must not merely be examined with the view of counting the corpuscles, and estimating the relative proportions of white and red corpuscles, although this gives valuable information, and can be readily done on recent specimens. But dried and stained films should also be minutely examined to determine whether the case is really one of leukæmia and not of simple leucocytosis. Dr. A. C. Coles relates a case (*The Blood, How to Examine and Diagnose its Disease*, London, 1898, p. 154) which shows the importance of this more rigid scrutiny. It was the case of a child, eleven years of age, with much enlarged spleen and slight enlargement of lymphatic glands. The red corpuscles numbered 3,458,333 per cubic millimetre, the white corpuscles 44,315 per cubic millimetre, or a proportion of 1:78, which might have been consistent with splenic anæmia. In stained films it was found that the "leucocytes, present very largely, consisted of typical marrow cells, and large eosinophile myelocytes were frequent." In that case the myelocytes formed 37.270 of the total leucocytes, and as time went on the proportion of white to red cells very much increased. In this case, as indeed occurs generally in leukæmia, there were a certain number of nucleated red corpuscles (normoblasts). It is conceivable that there may be no leucocytosis and yet leukæmia be present, if all or most of the white cells be of the abnormal type; and therefore it is all the more essential, before making a diagnosis of "pseudo-leukæmia," whether splenic or lymphatic, that the microscopical examination of the blood should be as thorough as modern methods permit.

During the course of the illness the degree of leucocytosis is liable to vary very much. It does not by any means always progressively increase, but, on the other hand, may diminish and even disappear. This change, whilst often harmonising with improvement in other respects, and possibly with justice attributed to the effects of treatment, is not always a sign of returning health. Indeed it is not seldom for the later stages of the disease to be marked by a considerable falling off in the number of leucocytes. *Per contra* a sudden increase in this may coincide with some inflammatory complication, in which case the rise is due to a true leucocytosis, *i.e.* an increase in the multinucleated cells. Lastly the leucocytes in this disease do not exhibit the amœboid movements which are so characteristic of the ordinary white blood corpuscles.

ACUTE LEUKÆMIA

It is a moot point whether the condition first described by Ebstein as "acute leukæmia" has a real relationship to the better-known and more slowly progressive disease. Pathologically it conforms to the type of "lymphatic leukæmia," and indeed Fraenkel went so far as to say that all the cases of lymphæmia were acute—a statement not borne out by the experience of others. Clinically its hæmorrhagic nature brings it into close relationship with purpura and scorbutic diseases.

Clinical characters.—The disease may begin abruptly with chills and pyrexia, or, after a week or two of malaise and headache with advancing anæmia, take on a more acute course. In most cases there is swelling of external lymphatic glands, especially the cervical, but the axillary and inguinal may also become enlarged. A series of five cases was reported to the Royal Medical and Chirurgical Society, in 1898, by Drs. Rose Bradford and Batty Shaw. All were male subjects, ages ranging from seven to fifty-eight years. In all the lymphatic glands were enlarged to a varying extent, and in the four cases in which post-mortem examinations were made, the lymphoid tissue of the intestines was also markedly increased. The thymus gland too was noted to be persistent. The spleen was not invariably enlarged, and never to any marked degree; but a noteworthy feature in these cases was the alteration in the bone marrow, which had a red gelatinous appearance.

The blood.—Leucocytosis was marked, being chiefly due (in three cases where such observations were made) to a preponderant excess of large uninucleated lymphocytes, the ordinary polymorpho-

nuclear cells being almost entirely absent in two of the cases ; more abundant, although much below the normal proportion, in the third. A few myelocytes were present in two cases. Thus, although as regards the blood these cases belonged to the lymphæmic type, yet the evident morbid change in bone marrow suggests as much a myelogenous as a lymphatic origin.

The symptoms of the affection, in addition to pyrexia and anæmia, consist in gangrenous stomatitis, swelling and ulceration of gums, and great liability to purpuric extravasations. The similarity to scurvy was still further heightened in one of the cases recorded by Drs. Bradford and Shaw by the fact that the patient, a youth of nineteen, had for two years previously abstained from fresh vegetable food, to which he had taken a dislike.

Some of these cases are very acute, running their course in a week or ten days, whilst even those in which the prodromal stage lasted a month or more, the total duration of illness seldom exceeded two months.

The number of cases hitherto recorded has not been large, and the disease is not amenable to treatment. Owing to the simulation of purpura, it is essential to the diagnosis that the blood should be carefully examined, and that a differential study of the leucocyte elements should be made.

The **diagnosis** of leukæmia rests mainly upon the results of the examination of the blood in association with enlargement of the spleen or of lymphatic glands. The diseases most likely to be confounded with it are the two forms of so-called *pseudo-leukæmia*—viz. splenic anæmia, and Hodgkin's disease. These are also chronic affections, but in neither is there as a rule any leucocytosis except in advanced stages, and the degree of anæmia is variable, nor does the spleen in Hodgkin's disease ever attain the large proportions of the leukæmic spleen. More difficulty may arise in the acute disease, which has doubtless often been referred to other affections. Its resemblance to purpura or scurvy has already been sufficiently alluded to ; but its frequently febrile course, and the occurrence of diarrhœa, with some swelling of the spleen, may lead it to be mistaken for enteric fever, or for malignant endocarditis, to which the hæmic murmurs that may be present, as well as the anæmia and purpura, may also give some countenance. Here again the value of the examination of the blood, and especially of stained blood films, is of the greatest importance in the diagnosis.

The **treatment** of leukæmia has undergone some changes, in accordance with the varying views as to its pathology. Thus when

the spleen was considered to be the organ primarily at fault, measures directed to it were in vogue, such as the application of cold in the splenic region by compresses or ice-bags; the inunction of absorbi-facient ointments, of which the iodide of lead may be taken as an example; the application of electricity or even of electrolysis. The radical measure of splenectomy was not only advocated, but even practised in some cases, with invariably fatal results. It may, however, be confidently asserted that no treatment directed to the spleen itself has any influence on the disease, and resort must be had to the use of internal remedies known to have some influence upon the blood itself. Amongst these *arsenic* is the chief remedy. We have seen its efficacy in pernicious anæmia, and shall have to mention its use in Hodgkin's disease; whilst in respect to leukæmia there seems to be some evidence that, for a time at least, it may arrest the progress of the disease. It is, as a rule, well borne, but it is advisable from time to time to intermit its prescription, and this must always be done if any signs of gastro-intestinal irritation should arise. That caution in its administration is needful is evident from the liability of some leukæmic patients to suffer from gastric or intestinal hæmorrhage, whilst diarrhœa is by no means uncommon. The simplest method of administration is by means of the liquor arsenicalis, commencing with a small dose (5 minims t.d.s.) and gradually increasing this (up to 15 minims t.d.s.), given always after food. The cutaneous pigmentation which is so often seen in leukæmia, deepening as the disease advances, may in part be owing to the long-continued use of this remedy. The action of the drug may be tested by the blood count, but it must not be forgotten that leukæmia, like pernicious anæmia, is subject to periods of remission, and a great fall in the number of leucocytes, even to the extent of the disappearance of leucocytosis, may take place temporarily. About twenty-five years ago Dr. Wilson Fox suggested the prescription of *phosphorus* as a remedy for leukæmia, and published a case which appeared to justify its use. It was given in the free state in pill in dose of $\frac{1}{20}$ to $\frac{1}{50}$ grain; but experience did not confirm the favourable opinions at first formed, and in a few years it was practically abandoned, especially as there was reason to believe it responsible for exciting albuminuria and hæmaturia. More recently the treatment of leukæmia by *oxygen inhalations* has been practised—from 30 to 60 litres a day being used in most cases—and the records show a striking amelioration, as evidenced by a rapid fall in the number of leucocytes, and a shrinking of the spleen. But sometimes arsenic was given as well, which vitiated the results of the

therapeutical experiment, and in cases where apparent cure resulted, the diagnosis of leukæmia, rather than one of pseudo-leukæmia, (splenic anæmia) is doubtful. Nevertheless more cases have been recorded of benefit (temporary though this may have proved) than of lack of improvement; and sufficient warrant has been given to justify the continued use of the remedy. At the least it may do some good by promoting metabolism, and checking the downward course of the malady.

The general measures to be adopted are those which are useful in all anæmic maladies,—fresh air, rest, good diet—form the essentials of the treatment; whilst it often happens that complications call for an interruption of the special line that is being pursued in order that remedies appropriate to them may be given.

SPLENIC ANÆMIA

Mention has already been made of the somewhat incongruous group of affections which have from time to time been described as “splenic anæmia”; and it must be confessed that there is great difficulty in presenting a clear picture of the disease as a clinical entity. The confusion is no doubt due to the fact that a combination of anæmia with enlargement of the spleen is by no means infrequent. It has long been known as a sequel to malarial infection, where the term “splenic or paludal cachexia” is almost classical. If all such cases are to be regarded as examples of “splenic anæmia,” then our conception of the condition would be far wider than many writers on the subject could admit. The term has moreover been freely applied to the cases that occur in infancy and early childhood, mostly in association with rickets and congenital syphilis, yet apart from the presence of the two essential factors which give the name to the disease, such cases clinically run a different course from the condition in the adult to which “splenic anæmia” is by many restricted. It is necessary to mention this, because there seems to be little doubt that the cases of “infantile splenic pseudo-leukæmia” to which Von Jaksch drew attention are almost confined to the rachitic and syphilitic series with which we are familiar in this country. In these cases the blood presents a marked diminution in red corpuscles, with poikilocytosis, and constantly large numbers of normoblasts and even megaloblasts, whilst leucocytosis is also a feature, observers differing as to the incidence of the increase being on the polynuclear cells or the lymphocyte elements. Stengel, to whose summary we are indebted for these facts, demurs

to the condition being regarded as a clinical entity, and regards it rather as a "type of secondary anæmia which may occur in consequence of a variety of affections, and which owes its peculiar characters, and in particular the marked leucocytosis, and the number of nucleated red corpuscles, to the age of the patients, rather than to an underlying disease." It need only be here added that this condition is very amenable to treatment, thereby differing markedly from true leukæmia, with which it may be confounded, as well as from the cases which occur in later periods of life, and to which the term "splenic anæmia" is more rightly applied.

Clinical characters.—Nevertheless there is considerable variety in the clinical features of splenic anæmia apart from the infantile cases. Thus in some the degree of anæmia may be comparatively slight, perhaps not so much as in leukæmia; but there is a progressive enlargement of the spleen, with increasing asthenia, and liability to hæmorrhages, especially gastric, and a duration of symptoms lasting for from two to five years, or even longer. These are the cases which are most likely to be confounded with splenomyelogenous leukæmia; and it is only the microscopical examination of the blood that serves to distinguish them. For there is not only no leucocytosis, but there may be even a diminution below the normal number of leucocytes. The writer has seen one such case, which occurred in a woman between forty and fifty years of age, who had never been exposed to malaria, but had had rheumatic fever, and three difficult labours, after one of which she took cold and suffered from what she termed "ague." There, however, had been no recurrence of the attack, and the first indication of the malady from which she died was swelling of the left side of the abdomen. A splenic tumour was detected, which for upwards of two years continued to increase, until it filled the left half of the abdomen from the xiphoid to the pubes, reaching beyond the middle line at the umbilicus. There were occasional attacks of pain over the organ, but except for a progressive asthenia and emaciation, the case was very free from complications. The blood was examined on several occasions, but no leucocytosis was ever observed; nor was the anæmia at all pronounced. Death occurred from exhaustion nearly three years from the date of the first complaint of the splenic swelling. This case is exceptional, for in most other examples of splenic anæmia of as long duration there have been attacks of hæmorrhage from stomach and bowels, sometimes recurring and of considerable gravity. In other cases diarrhœa, and in others ascites have materially added to the enfeeblement of the patient.

The other type of splenic anæmia runs a briefer course, most of the cases terminating fatally within two years or less of their inception. The anæmia may become very profound, being increased by the liability to hæmorrhages, such as epistaxis, or bleeding from slight traumatism, as if a hæmophilic tendency had been developed. The illness is further markedly pyrexial—the type of fever being very irregular—herein contrasting with the more chronic type first mentioned. There may be digestive disturbances, attacks of vomiting or of diarrhœa, or constipation may be troublesome. The spleen may enlarge to dimensions equal to those seen in typical leukæmia, and, as in that disease, attacks of pain may occur over the splenic region, where there is mostly some tenderness.

Examination of the blood shows a very considerable diminution of the red corpuscles, and in some cases poikilocytosis (Williamson, Osler) was seen; whilst in the greater reduction of hæmoglobin the blood conforms to the chlorotic type. There is mostly no abnormal change in leucocytes, but in a case recorded by Dr. S. West there was marked leucocytosis (50,000 per cub. mm.), chiefly of lymphocytes, which, owing to the great reduction in red corpuscles (2,055,000), gave a ratio of 1 : 40. At first sight such marked leucocytosis might raise doubts as to the propriety of regarding the case as one of “splenic anæmia” rather than “leukæmia,” but, as Dr. West points out, the great reduction in the red corpuscles makes the excess of white cells more apparent. Besides the febrile as well as hæmorrhagic character of this case may have contributed to raise the leucocyte count. It is exceptional to meet with any leucocytosis, except at an advanced stage; as a rule these corpuscles may be even below the normal numbers.

Diagnosis.—The chief disease to be distinguished is leukæmia, or rather its spleno-myelogenous form. The clinical characters may closely resemble those of leukæmia, and the spleen may attain equally large proportions. The blood examination should suffice to make the distinction, for in splenic anæmia leucocytosis is exceptional and mostly quite lacking, whilst the characters of anæmia are often more pronounced than in leukæmia. Simple enlargement of the spleen, malarial or other, syphilitic and amyloid disease, may not always be readily distinguished, especially as anæmia is very likely to be present also. In such cases the history may be of value in forming the diagnosis, as well as the fact that the organ does not in these affections continue to increase in size to the extent that is here seen, an extent which has led some authors to term the condition “splenomegaly.” The enlarged spleen

met with in some cases of cirrhosis of the liver might be mistaken for "splenic anæmia" in its more chronic types, and the occurrence of hæmatemesis may further obscure the diagnosis, which must depend rather upon the other concomitants of the hepatic affection, such as an alcoholic history, diminished liver dulness, and marked ascites, rather than upon any obvious characteristics of the splenic enlargement and the condition of the blood. From Hodgkin's disease, in which the spleen is often enlarged, the absence of any implication of lymphatic glands is the chief point of distinction. Both these affections have been termed "pseudo-leukæmia," but in the one the spleen, and in the other the lymphatic glands, appear to be the primary sources of the anæmia.

Treatment, in most cases, and especially those of the acute or subacute type, is little else than palliative. The ordinary lines of treatment of anæmia are to be pursued, varied as may be necessary in the face of complications. The only point on which it is necessary to remark is one of great importance, to which Banti (who in 1882 first described "splenic anæmia" as a distinct disease) called attention. If the anæmia be—as the history of the cases would seem to show—secondary to the splenic disease, might not splenectomy be resorted to in the hope of arresting the malady? The operation of splenectomy for the removal of hypertrophied or floating spleens has been successfully performed without any ill results to the patient from the loss of the organ; and it would seem to be justifiable and hopeful of good result in the cases of splenic anæmia which run a protracted course, although in the more acute and febrile cases there is ground for fear lest such an operation might be as dangerous and therefore as unjustifiable as in leukæmia itself.

HODGKIN'S DISEASE

SYN. LYMPHADENOMA

In lymphadenoma or Hodgkin's disease (so named after Dr. Hodgkin of Guy's Hospital, who first described it in 1832) the characteristic clinical features are progressive painless enlargement of the lymphatic glands, enlargement of the spleen, associated with anæmia and fever of an irregular type. It is not a well-defined affection, owing to the close relationship it bears to leukæmia and to splenic anæmia, on the one hand, and to the form of malignant disease known as lymphosarcoma on the other. There is, however, ample justification for its separation from these conditions, to which

its resemblance has been recognised in the use of such terms as "pseudo-leukæmia" and "malignant lymphoma" (Billroth), sometimes employed to denote it.

Clinical characters.—Occurring mostly in early adult life, but by no means limited thereto. The earliest clinical indication of the affection is the *enlargement of lymphatic glands*, generally an external group, for example the cervical. There may at first be no suspicion that it is anything but a localised lymphadenitis, to which view further support may be given by the previous existence of some primary source of irritation, such as ulcerative tonsillitis, or cutaneous inflammation. When this is so, indeed the case can hardly be regarded as of specific nature, and weeks or months may elapse before the lymph-glandular affection ceases to be a local and becomes a general disease. Contrasting with such cases there are others in which the glandular enlargement very rapidly involves more than one region, and it is on the occurrence of such generalisation that the true nature of the malady is revealed. Thus, starting in the cervical group, the glands first of one side are involved, then those of the other; and almost synchronously, or at a slight interval, the axillary and the inguinal glands may take on the change. It is usual for the disease to begin in the neck, but it may start in the groin; whilst there is great variability in the extent to which any particular gland chain is affected. Nor is the disease limited to external glands; it may equally fall, and sometimes from the first, upon such important groups as the bronchial, mediastinal, retro-peritoneal, and mesenteric. Further, other lymphoid structures may share in the general hyperplastic tendency, especially those connected with the gastro-intestinal tract, including the tonsils and the widespread lymphoid tissue that pervades the small and large intestines (see p. 326). Many of the symptoms of the disease depend therefore upon the particular region of the body in which this lymphatic overgrowth occurs, and the case may in its course be complicated by the local derangements thus arising.

As regards the appearance of the glandular swellings, there is as a rule nothing very distinctive about them. That they are glandular there can be no question; for each swelling can be felt to consist of a closely packed congeries of firm, smooth, rounded or oval masses varying in size from a pea to a pigeon's egg. They are neither painful nor tender, unless, as sometimes happens, some inflammation arises within them; and the tumour may throughout retain its lobulated character and be free from adhesion to the skin. Often, however, as time passes, the swelling becomes less well

defined, and the outlines of individual glands less readily made out, whilst the skin becoming adherent the whole mass appears to be fixed. Such a change is generally more marked in the cervical region than elsewhere, and is due to the infiltration of the lymphoid cells through the gland capsules and beneath the skin. Similar change may occur in the case of the internal group when these are involved, but its detection is of course not possible, the signs of the continued enlargement and diffusion of the gland mass being those of interference with function of adjacent organs and structures that are subjected to compression.

Although the enlarged glands in Hodgkin's disease do not tend to suppurate or caseate, they yet vary somewhat in consistency, and this mostly in concordance with the greater or less chronicity of the attack. In the slowly progressive cases the glands as a rule are firm and solid; but in the more rapid cases they have a soft, elastic feel, and may even give the sense of fluctuating. This difference in consistency depends on the relative amounts of cells and stroma, and the tenuity or density of the capsules of the enlarged glands.

Next to the glandular affection the most striking characteristic of Hodgkin's disease is the *anæmia*. This may be very marked indeed, the pallor of skin and of the visible mucous membranes being most conspicuous. There are few cases in which there is no such anæmia, but some have been recorded where the number of blood corpuscles has been only slightly below the average. Such cases are, however, exceptional, the reduction in red corpuscles being often considerable, although not reaching the extreme limits observed in pernicious anæmia. The usual degree of reduction is from 50 to 60 per cent of the normal, when the disease is fully pronounced. The percentage of hæmoglobin is generally, as in chlorosis, below that of the corpuscles, so that the colour index is low. In typical cases no change is noticeable in the white corpuscles, which are about as numerous as in health; but in an advanced case there may be some degree of leucocytosis, which is more commonly due to an increase of the multinuclear neutrophile cells, as in inflammation, than of any other element, such as the lymphocytes. Still cases in which this lymphocytosis does occur have been related, rendering the distinction, at this stage of the illness, from lymphatic leukæmia almost impossible.

Pyrexia is an almost constant feature of the disease, being more marked and more hectic in type in the rapid cases than in those which are more chronic; but it is seldom entirely lacking in the

latter, and, although fairly continuous, its course may be marked by exacerbations lasting for a week or two and then subsiding. Or the course of the fever may be interrupted by periods of apyrexia, giving the chart the characters of a relapsing fever. Profuse sweating may accompany the fever, but usually the skin is dry.

The patient early complains of lassitude and physical weakness, the *asthenia* increasing as the case advances, when also *œdema* of the lower extremities may set in, owing to feebleness of the circulation. The *pulse* thus shows a tendency to increase in rate, and to become more compressible, whilst the cardiac sounds become weaker in intensity. Hæmic bruits are often to be heard. There is a liability to hæmorrhages, especially epistaxis, as in leukæmia, but, in the writer's experience, not nearly so marked as in that disease.

There is nearly always considerable *emaciation*, which is most marked in cases where the pyrexia has been fairly high, and where gastro-intestinal derangements are prominent. For in some cases—e.g. those where the digestive tract is specially involved—diarrhœa may be a troublesome symptom.

The *urine* may present no change in the earlier stages, but it is not uncommon for albuminuria to appear in the later periods.

As above stated, many symptoms may be superadded, or may, indeed, form the prominent feature of the illness when the internal glands are involved. This is especially the case when the intra-thoracic glands are those which undergo enlargement, for then all the signs and symptoms of mediastinal tumour may arise, such as dyspnœa from pressure on the trachea, dysphagia from pressure on the œsophagus, enlargement of superficial veins from pressure on the vena cava or innominate veins, hydrothorax from pressure on the vena azygos, inequality of pupils from pressure on the sympathetic. In addition to these *pressure signs* physical examination will reveal the signs of mediastinal tumour. If the abdominal glands be enlarged, they can generally be made out by palpation, and their presence may give rise to jaundice and ascites by pressure on the structures forming the hilus of the liver. A case has been recorded where paraplegia arose from compression of the spinal cord by intrusion of lymphoid growth into the vertebral canal. Abdominal examination also reveals the existence of an *enlarged spleen*, and this quite apart from any affection of the abdominal lymphatics. The splenic tumour does not attain a large size, but is usually to be felt projecting for a distance of 2 or 3 inches below the ribs, its firm sharp border, with its characteristic notch, being mostly readily appreciated.

There must also be mentioned the occasional but rare occurrence

of *lymphoid growths in the skin*, the counterparts of similar nodular formations met with in the substance of the internal viscera in this disease. The occurrence of *pigmentation* of the skin to an unusual degree has been noted in abdominal lymphadenoma, and has been attributed to pressure upon the solar plexus and abdominal sympathetic. The pigmentation may be almost as marked as in Addison's disease, but the suprarenal capsules are not affected. Hence such cases seem to support the view that the melasma of Addison's disease may depend on the involvement of the abdominal sympathetic. The explanation of the pigmentation being due to arsenical medication is hardly tenable in view of the fact that the use of this drug is by no means limited to the cases where abdominal glands are the seat of enlargement. As in other anæmic diseases, purpuric eruptions not infrequently occur on the extremities, and perhaps also on the trunk, mainly in the more acute cases.

Course.—The duration of Hodgkin's disease is variable. Some cases are very slow in their development, if reckoning be made from the time of the first appearance of a lymphatic swelling. For such a swelling may remain for months, or even years, as a purely local affection, and then but gradually, with alternating periods of growth and arrest, other glands may enlarge. In contrast to such cases are those in which the whole course of the disease, to its fatal termination, is traversed within one or two years, and much more rarely the acuter class, where duration is reckoned by months, or even weeks. Whether true recovery ever takes place in the sense of entire subsidence of the lymphatic overgrowth is perhaps doubtful, but certainly in the more chronic class first mentioned the case often passes away from observation after having been apparently stationary for a long period.

Although we have described this affection with the diseases of the blood, with which it seems to have many affinities, it is a moot point whether it has not even closer relationship to diseases of the lymphatic glands. Certainly as regards **diagnosis** it may be more difficult to differentiate it from affections of the latter class, at any rate in its early stages, than from the former. If simple lymphadenitis be set aside from the absence of any infecting focus to account for the swellings, Hodgkin's disease may be simulated by syphilitic, tuberculous, or sarcomatous affections of the glands. The history of the case, the associated signs of specific taint in syphilis, the tendency of tuberculous glands to soften, and the concomitance of other tuberculous lesions may serve to differentiate the two former affections, as well as the rarity for multiple groups

of glands to be involved in them. It may not be so easy at first to discriminate lymphosarcomatous growths, but it has been pointed out that in this affection the blood shows an excess of lymphocytes, a character that it does not present in Hodgkin's disease. From the other blood diseases the differentiation of Hodgkin's disease is fairly easy. The only one with which it is likely to be confounded is lymphatic leukæmia, and that only when Hodgkin's disease exhibits leucocytosis. But in Hodgkin's disease such leucocytosis, if it occur at all, is a late event in its course, and is mostly confined to the multinuclear cells. In lymphatic leukæmia it is the leucocytosis which stamps the affection throughout, and it is emphatically a lymphocytosis, the multinuclear cells being mostly below the normal in number.

The **treatment** of Hodgkin's disease follows much the same lines as those pursued in other anæmic disorders. Rest, fresh air, nutritious and wholesome diet are leading principles in all these affections, whilst the ordinary hæmatinic remedies, such as iron, are frequently prescribed with advantage.

It is noteworthy also that in this disease, as in those previously considered, the value of arsenic as a remedy has been given a high place. Nor is its administration confined to oral exhibition. Several physicians have recommended and practised the injection of a few minims of liquor arsenicalis into the gland substance, and have described very marked results therefrom, notably in the marked subsidence of the swelling. There is, however, some risk of causing inflammatory reaction by this procedure, which has not been much resorted to in this country. The administration of free phosphorus has been said to give good results, as in leukæmia, but the objection to its continued use arising from its action in inducing albuminuria is sufficient to require that it should be but sparingly and cautiously prescribed.

In the early stages of the affection the extirpation of the enlarged glands might *a priori* seem to be justified, but the hopes that are thus raised that the affection will be prevented from progressing have been invariably disappointed. Sooner or later other glands will enlarge, and even repeated surgical operations fail to overtake the tendency to this progressive change. Hence such operative interference, at one time much recommended, has fallen into desuetude. Indeed, there is reason to believe that it may operate rather as a stimulus than a check to the further development of the affection. Nor is much, if anything, gained by the application of absorbent remedies to the skin over the site of the enlarged glands, such as

iodide of lead, or iodide of potassium, and belladonna ointments, or painting the surface with tincture of iodine. Cold compresses or the application of cold by means of Leiter's coils, or ice-bags have been equally tried, but with little permanent effect in controlling the growth of the glands.

B. THE HÆMORRHAGIC GROUP

HÆMOPHILIA—PURPURA—SCORBUTUS—PAROXYSMAL HÆMO-
GLOBINURIA

HÆMORRHAGE, besides being the most common and obvious cause of anæmia, is also, as we have seen, a not infrequent result of that condition, notably in pernicious anæmia and leukæmia. It would appear as if the blood state in these affections induced vascular deterioration leading to the rupture of capillaries and small vessels, and this to such an extent sometimes as to mask the original affection. The diseases we have now to consider are of a different category, for in them apparently such vascular deterioration or hæmorrhagic tendency is the most prominent feature, accompanied or followed, rather than preceded, by more or less marked anæmia.

Symptoms and effects of hæmorrhage in general.—It may be convenient if, before describing the symptoms of these hæmorrhagic affections, brief reference were made to those of hæmorrhage in general and of concealed or internal hæmorrhage in particular. As Dr. S. West has pointed out, the supervention of hæmorrhage, *e.g.* hæmoptysis or hæmatemesis, is not infrequently preceded by local *pain*, referred more or less precisely to the spot whence the bleeding takes place some hours or even days after this pain is experienced. The explanation of this premonitory symptom is not clear. In the case of pulmonary tubercle it might well be that local turgescence precedes rupture of vessels and compresses nerves; but that such antecedent congestion necessarily precedes the erosion of blood-vessels by a gastric or intestinal ulcer is not easy to conceive, for the pain referred to is not that which characterises the ulceration *per se*. The occurrence of the hæmorrhage relieves the pain, a fact in favour of the congestive hypothesis. In the case of deep-seated aneurysms, which rupture into serous sacs or into the alimentary or respiratory channels, pain is so essentially a feature of the pressure of the aneurysm upon the structures it invades, that not much significance can be applied to its occurrence before the actual

rupture takes place. Dr. West's observation is, however, one worth bearing in mind, especially in cases of pulmonary tuberculosis.

The symptoms of hæmorrhage, apart from local indications of its source, vary according to its amount and mode of occurrence. A sudden and profuse escape from internal blood-vessels may be followed within a few minutes by death from *shock* or *syncope*, the marked pallor of the surface alone suggesting the cause of this almost sudden death. But so rapid a termination is not usual even in fatal hæmorrhage, for the reason that the conditions which produce it do not allow of the sudden emptying of blood-vessels, which must take an appreciable time, measured perhaps by minutes rather than hours. During this interval between the commencement of the bleeding and the fatal issue, the patient, whose pallor becomes more and more marked, does not at first lose consciousness, but the pulse becomes very rapid, small and thready, and the temperature of the body falls below the normal, the respirations shallow and gasping, and unless the bleeding be arrested, or the vascular tension restored by transfusion, syncope may supervene.

In cases of severe but non-fatal hæmorrhage similar effects are produced, and syncope may even take place; but the cessation of the bleeding occurs before depletion has reached a fatal limit. A condition of general œdema, even extreme, not infrequently supervenes. Recovery from such extreme blood-loss may be slow, but it is remarkable to what an extent the loss may proceed, and yet restoration take place.

Women bear severe blood-loss better than men, and although long retaining an almost exsanguine appearance (*e.g.* after severe hæmatemesis or post-partum hæmorrhage), there is a gradual return to the previous state. The reaction after such hæmorrhage may be marked by a distinct *rise in temperature*.

Besides these acute hæmorrhages there are those which occur in less amount but intermittently, inducing a more or less persistent state of anæmia and physical weakness. It is doubtless in part to repeated, though small, hæmorrhages that the cachectic appearance of many cases of malignant disease is due.

As regards the actual *state of the blood* in hæmorrhage, much depends upon the nature and extent of the latter. There is a considerable—it may be an excessive—reduction in the number of red corpuscles, which in the “chronic” cases referred to may remain permanently much below the normal standard. After an acute and severe but non-fatal hæmorrhage it is not long before indications of a re-inforcement of the blood in these elements appear. For mingled

with small immature microcytes, and evidences of degeneration in the presence of poikilocytes and chromatophilic corpuscles, are to be seen many normoblastic nucleated corpuscles in the circulating blood, testifying to the call made by the losses upon the regenerative activity of the hæmopoietic organs. But what is perhaps a more characteristic feature of this post-hæmorrhagic anæmia is the occurrence of *leucocytosis*. Within a very short time of the depletion, the leucocytes (multi-nucleated form) may be observed to be increased, not only relatively but actually. It is also pointed out that, especially in cases of repeated hæmorrhages, the blood-plates are increased in number.

HÆMOPHILIA

Examples of this remarkable affection are more likely to come under the notice of the surgeon than of the physician, since its essential feature is a proneness to hæmorrhage, of a severe and often uncontrollable character, from comparatively slight injury. There is, however, a tendency to spontaneous as well as to traumatic hæmorrhage. Happily of rare occurrence, hæmophilia affords one of the most striking examples of inherited transmission in the nosology. This is denoted by the alternative term applied to it, namely, the "hæmorrhagic diathesis," and families, the members of which display the tendency, are often spoken of as "bleeders." Its pathology is obscure, but the nature of the affection is such as to reasonably suggest that the congenital defect is one of undue delicacy in the structure of blood-vessels, with possibly also a diminution in coagulability of the blood. If such be the case, and there can hardly be said to be positive proof that it is so, the affection would rank with congenital malformations and other errors in development. Its position amongst "diseases of the blood" must be only provisional; it can hardly be said to be pathologically proven.

It is mainly confined to males, a sexual selection which is curiously paralleled by other notable inherited disorders, as pseudo-hypertrophic muscular paralysis and colour-blindness. But this is not all, for in all these affections, although the daughters of the family may escape the proclivity, they transmit it to their male progeny. This liability of the males to suffer from the defect, and the transmission of the latter through the unaffected females, are not invariable, but common enough to raise grave doubts as to the propriety of permitting the girls of such families to marry. It is equally important, in view of prophylaxis, that no hæmophilic male

should marry. As regards the extent to which the hæmophilic tendency may be transmitted, there are well-established data which show that it has been handed down for generations like other ancestral qualities. On the other hand, the tendency may sooner or later seem to wear itself out.

The accompanying diagram, which is copied from one given by Lossen (*Deutsch. Zeitschr. f. Chir.* Bd. 7), illustrates the transmission of the hæmophilic tendency through three generations. Klebs, in reproducing the diagram, points out that it shows how the tendency is

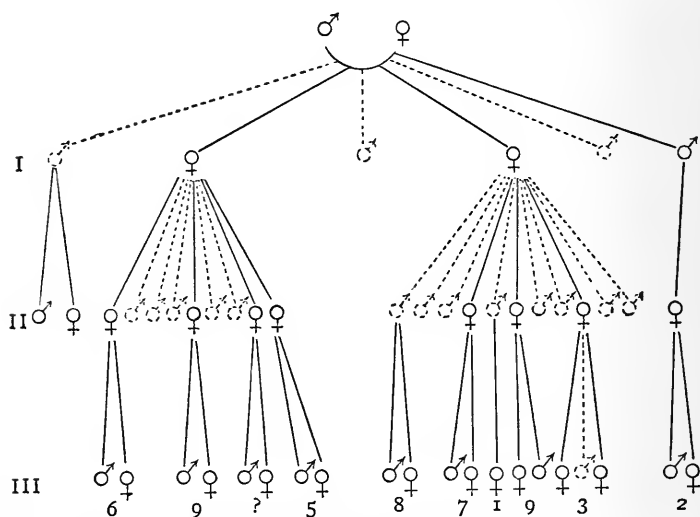


FIG. 21.—Genealogical tree of the Mempel family (after Lossen). All the hæmophilic subjects are males; they are indicated by dotted lines.

here exclusively transmitted through the female members, who are themselves exempt. But there are three hæmophilic males whose marriages with non-bleeders were not followed by any transmission of the tendency. Possibly—nay, very probably—could the genealogy be further traced, the daughters of these hæmophilics might have given birth to hæmophilic sons. The diagram shows that of the four sons in the first generation three were hæmophilic; that in the second generation every male child of the two females of the first generation was hæmophilic, thirteen in number, whilst the seven daughters were exempt. The third generation, which numbered at least fifty individuals of both sexes, only contains one hæmophilic, and he a son of a non-hæmophilic daughter of the second generation. There are even more

striking genealogies published than this, which seems to show, as Klebs suggests, the weakening and possible elimination of the inherited taint as early as the third generation; but who can say whether subsequently there might not arise an atavistic return to the diathesis?

That some checks operate to prevent the indefinite transmission of this tendency is obvious; since, were it otherwise, hæmophilia would surely be far more common than it is. There is a natural check in the fact that a considerable proportion of hæmophilics do not attain maturity, but nevertheless a sufficient number of them marry and have children to transmit the taint in an ever-widening circle, unless through repeated marriage with non-bleeders the diathesis becomes practically set aside.

Symptoms.—In a certain proportion of cases (according to Grandidier as many as 82 per cent or 93 out of 113 cases known to him) the hæmophilic tendency reveals itself before the end of the third year of life; but there must not be included in such those cases of spontaneous hæmorrhage in the newly born, which do not belong to the category of hæmophilia. Indeed most writers aver that it is in childhood and early boyhood rather than in infancy that it first makes its appearance, when, that is, exposure to trivial injuries becomes frequent. The slightest blow may be followed by extensive bruising; a cut finger give rise to serious hæmorrhage. Fatal results have followed the extraction of teeth, all efforts to check the bleeding being without avail. It is not so much the rapidity of the loss, but its prolonged continuance as a general oozing, which depletes the vessels and may lead to syncope or death by exhaustion.

Of *spontaneous hæmorrhages*, epistaxis is by far the most frequent, and is again mainly to be met with in the period of adolescence, as indeed is the case also in non-hæmophilics. The readiness with which this bleeding is provoked, and the great difficulty there is in arresting it, are the chief characteristics of the epistaxis of hæmophilia. Other mucous surfaces may be the seat of similar efflux of blood, as the mouth or fauces, the bronchial tract or the gastro-intestinal, the attacks of hæmoptysis, hæmatemesis, or melæna arising without apparent assignable cause. Sometimes hæmaturia occurs. Purpuric eruptions, or even large areas of subcutaneous hæmorrhage, may appear apart from any blow or other injury. Hæmorrhages into serous sacs—pleura, pericardium, peritoneum—have been known to occur and constitute grave complications. The attacks of joint-swelling to which the hæmophilic is liable, especially of the knee-joints, simulating arthritis, are doubtless to be ascribed to hæmorrhage occurring

into the synovial sacs from the vascular fringes on the interior of the joint.

To enumerate all the ways in which the life of a "bleeder" is imperilled would occupy much space. There are authentic instances of serious and sometimes fatal results from such trivial procedures as the rite of circumcision, the performance of vaccination, the prick of a pin, the opening of an abscess. It is often only by the utmost vigilance and circumspection that the child grows to be a youth, and the youth to manhood. It is doubtful if he can ever outlive the tendency, although he may reach to maturity after many a perilous passage. Recurrent attacks of synovitis may result in permanent enlargement and stiffness of the joint. Lastly, if not carried off by the effects of injury, or reduced to extreme asthenia by repeated blood-loss, he may die from an attack of internal hæmorrhage, *e.g.* in the brain.

It is an interesting fact that prior to the occurrence of an attack of spontaneous hæmorrhage or arthritis, the patient may be feeling physically at his best. This has led to the suggestion that a state of plethora may be the immediate antecedent and perhaps the proximate cause of the hæmorrhage.

The **diagnosis** of the condition is not difficult, provided the previous history of the patient be known. There is nothing specially distinctive about the hæmorrhages *per se*; it is rather their mode of occurrence and repetition, as well as their intractability, that arouse suspicions as to their true nature. The sex of the patient and the liability to attacks of arthritis of the knee-joint are factors in arriving at a diagnosis.

Prognosis is always grave as regards the issue of an attack of hæmorrhage; whilst the prospect of attaining maturity depends largely upon the kind of life that is led and the amount of care and protection that can be afforded him.

Treatment.—In the first place comes the practice of prophylactic measures. Bearing in mind the sexual incidence of the inherited taint, it is in respect to the male children of these families that such measures must be adopted. They consist mainly in the careful safeguarding against injury, or the infliction of even slight wounds for surgical reasons. Thus the hæmophilic taint ought to be considered a bar to such trivial operations as vaccination, lancing of gums, circumcision, or extraction of teeth. Some of these or analogous procedures may come to be unavoidable, and in that case every means will have to be adopted to arrest the ensuing hæmorrhage, often very difficult to effect. The patient must be kept

absolutely at rest ; the application of cold, of compresses, and of styptics, such as the perchloride of iron. In cases of spontaneous hæmorrhage, enforced rest in bed, and the administration of ergot or of astringents, as hamamelis, turpentine, gallic acid, sulphuric acid, the perchloride or acetate of iron, may be tried. Coagulation is said to be facilitated by the administration of lime salts, especially the chloride of calcium ; and a solution of gelatine applied locally and by subcutaneous injection have been used for the same purpose.

An old practice, and one recommended by most physicians who have had the care of hæmophilic subjects, is the occasional prescription of mild saline purgatives, as the sulphates of sodium or magnesium. One indication for their use would be the sense of well-being which so often precedes an attack of hæmorrhage.

The general care of the hæmophilic consists in his leading a quiet life, with a spare diet, and attention to everything that promotes health, such as cold bathing, gentle open-air exercise, avoidance of stimulants and of excitement of any kind. Tonics, as arsenic, iron, and cod-liver oil, may also be taken.

PURPURA

It has been already pointed out that the symptoms of purpura may arise from many conditions, including mechanical obstruction to the circulation, the presence of toxic agents in the blood, some mineral (as the iodides), others organic (septicæmia, malignant fevers), others embolic (as malignant endocarditis), and others again due to diseases of the blood, including scurvy, leukæmia, pernicious anæmia. Even when these and other causes of secondary purpura are excluded there yet remain some affections, the pathology of which is still obscure, and it is to these that attention will now be directed. They are named purpura simplex, purpura rheumatica, and purpura hæmorrhagica, and their relative severity corresponds with the order in which they are enumerated.

PURPURA SIMPLEX

In this affection slight malaise, loss of appetite, occasionally sore throat, and pain in joints may precede the cutaneous eruption. This consists in the appearance of numerous small, scattered bright red or purplish spots, which do not fade on pressure and are not raised, the most usual sites being about the ankles and legs. The spots often occur in successive crops, and by their confluence may

form larger irregular areas. They may also appear on the trunk and upper limbs, where, however, they are seldom so abundant as on the legs. In two or three days they fade, leaving a yellowish-brown stain. The affection is more common in children and adolescents than adults, and is associated with some degree of anæmia and sometimes with diarrhœa. Relapses are common.

PURPURA RHEUMATICA

Known also as "peliosis," this form of purpura is more closely allied to the rheumatic diathesis than purpura simplex. It is moreover accompanied by more definite constitutional symptoms, *e.g.* slight pyrexia, as well as distinct, painful swelling of joints. The onset of the attack, which is marked by these manifestations, may be preceded by malaise and depression of some days' duration. The purpuric rash is mainly limited to the lower limbs, especially the front of the legs and around joints. In the former situation it may be combined with erythema nodosum, a variety to which the term "urticarial" has been applied. Occasionally vesicles form, and this variety is spoken of as "pemphigoid." The fading rash leaves a brown discoloration of the skin where the hæmorrhages have been, and relapses are exceedingly common, especially if the patient be allowed to get up too soon. During, and for some time after the attack, the patient may be markedly anæmic and be liable to gastro-intestinal disturbances. Some authors have noted the appearance of albuminuria, and others of endocarditis and pericarditis as complications.

Henoch described a form of purpura (since known by his name) which has some affinities with rheumatic purpura. It is more commonly met with in children than in adults, and a marked characteristic is the occurrence of attacks of gastralgia or colic with vomiting and diarrhœa. Hæmorrhages may occur from mucous membranes and also from the kidney, which may constitute a grave element of danger. The arthritic symptoms and the purpuric rash are very similar to those met with in purpura rheumatica, but the prognosis in Henoch's disease is not so favourable.

PURPURA HÆMORRHAGICA

This is the most severe type of the primarily purpuric affections, and were it not for the possibility of confusion with the hæmorrhagic forms of malignant fevers, it might with propriety be termed "purpura

maligna." It is more common in females than males, and, like all these affections, is a disease of comparatively early life, *i.e.* in adolescence and at early adult ages. There is apparently a proclivity to its development in individuals weakened by other illness, especially the chronic infectious diseases, as malaria, syphilis, and tuberculosis; and in those who live in states of squalor and insantiation.

In the most severe forms ("fulminans," Henoch) it develops with great rapidity; the hæmorrhages beneath the skin not long remaining as small discrete petechiæ, but forming more or less extensive areas which spread almost from hour to hour. Thus a great tract of subcutaneous hæmorrhage may exist over the thighs and buttocks, and spread to the abdomen and back. At the same time there is a proneness to hæmorrhage from mucous membranes—epistaxis, hæmatemesis, and melæna, as well as hæmaturia. Except as regards its origin, there is little to distinguish such a case from the most rapidly fatal form of hæmorrhagic smallpox. The result too is the same, death occurring from anæmia and exhaustion within a few days.

But all cases fortunately are not of this severity, although in most the purpuric manifestations are widely spread over the limbs and trunk, varying in size from petechiæ to considerable patches of ecchymosis. The actual occurrence of the purpura may be preceded by weakness, anæmia, and mild pyrexia. Constipation may be a feature of the illness. In these more favourable cases recovery may take place in about a fortnight, but convalescence is retarded by the anæmic state which has been developed.

In respect to the simpler forms of purpura, the question of diagnosis turns upon the absence of any of the numerous conditions in which petechial eruptions are liable to occur. If such conditions can be excluded, then the case may be considered to fall under the category of "purpura,"—a conclusion which will be further justified if the case be marked by rheumatic symptoms, especially joint pains and swelling. But there is more difficulty in arriving at a diagnosis of malignant purpura, owing to the close similarity borne to it by the malignant type of specific fevers, especially variola, by some cases of acute leukæmia and scurvy. The last-named disease may be excluded if there is no affection of the gums, although some of the predisposing conditions to scurvy are very similar to those of purpura hæmorrhagica. From leukæmia an examination of the blood should determine the distinction, bearing in mind, however, that there is, owing to the extensive

hæmorrhage, a state of anæmia with leucocytosis set up in severe purpura. The existence of epidemics of one or other of the specific fevers in the locality whence the patient comes may considerably influence the determination whether a "fulminant" case is due to such an infective disease, rather than to the special toxin which must be assumed to exist to account for such grave and extensive hæmorrhages.

The **treatment** of purpura is, it must be confessed, somewhat empirical. There is no doubt that relapses can be avoided by keeping the patient suffering from the simple or rheumatic forms long enough in bed; whilst for the latter the salicylates may be prescribed. Otherwise the treatment of such cases generally resolves itself into one of the administration of tonics, as arsenic and iron, and of nutritious food. It is doubtful whether any astringent remedies given internally, or the administration of oil of turpentine (10 minims per dose), or calcium chloride (20 grs.), do really check the hæmorrhagic tendency; but these latter drugs should certainly be tried in the worst cases. If there be any syphilitic or malarial taint, then it would be reasonable to prescribe the iodides in the former, and quinine or arsenic in the latter case.

SCURVY

SYN. SCORBUTUS

The cardinal **symptoms** of the scorbutic condition, namely subcutaneous and intermuscular hæmorrhages, with swelling of the gums and stomatitis, and the anæmic state that arises partly from the primary blood impoverishment, and partly from the hæmorrhage, are in most cases preceded by certain prodromata which extend over a week or more before these characteristic manifestations appear. Thus the subject of this malady begins to experience a lack of energy and physical vigour, and at the same time becomes also mentally dull and apathetic. He not only feels weak and ill, but he looks so, for the skin assumes a sallow, unhealthy tint. He suffers too from pains in the loins and limbs, sometimes from sore throat; but it is only rarely that at this early period any hæmorrhage, *e.g.* epistaxis, occurs.

The hæmorrhagic tendency of the disease is mostly manifested at first by a purpuric rash over the lower limbs, the eruption being scattered and petechial, confined for the most part to the region of the hair follicles. Very soon these punctate hæmorrhages are

supplemented by more extensive areas of subcutaneous bleeding, so that irregular purplish patches occur in various parts of the body, particularly about the thighs and buttocks. Firm brawny-like swellings in the calves of the legs, and in the flexures of joints, as the ham and the bend of the elbow, which are tender to the touch, denote the occurrence of hæmorrhage beneath fasciæ and between muscles, or even deeper still beneath periosteum, so that the patient becomes quite incapacitated. In some cases the knees and ankle joints will become swollen with effusion. The eyelids may become puffy and sub-conjunctival ecchymosis appear.

Associated with these hæmorrhagic signs there occurs early in the attack marked swelling and sponginess of the gums, which bleed very readily, and may form considerable fungating masses around the teeth, that become loosened, the change being most apparent around the incisors. In a severe case this condition passes on to ulcerative stomatitis, and the breath acquires a very fetid odour.

Epistaxis may now frequently occur, as well as spontaneous hæmorrhages from other mucous surfaces, such as the stomach and intestines, but hæmaturia is of rare occurrence.

The general condition of the patient is one of extreme debility and anæmia. The face, with its earthy, sallow complexion may, as the disease progresses, become bloated and unsightly. There is increasing emaciation, with œdema of the feet, and no abatement in the painful swellings of the limbs. The state of mental and physical languor becomes more marked; any exertion is irksome, and is accompanied by breathlessness and palpitation. Attacks of syncope are liable to occur. There is no pyrexia, and, except in advanced stages of severe cases, the urine remains free from albumen.

The physical signs of profound anæmia are present; there are hæmic bruits, and the blood may in severe cases show a very marked diminution in red corpuscles, with probably some leucocytosis. Coles says (*Dis. of Blood*, p. 187) that "usually, when anæmia is pronounced, poikilocytes and polychromatophilia are seen, and in cases in which extensive hæmorrhage has occurred, alterations in size and shape, as well as the presence of numerous nucleated red cells, may be very conspicuous."

An interesting symptom which was long since noted as occurring in scurvy is that of night-blindness, but that it has not any special relationship to this disease, other than functional exhaustion of the retina in a subject whose vital powers are greatly reduced, is now held to be the case by leading authorities.

If the case proceed to a fatal termination, this event may occur through cerebral or meningeal hæmorrhage, convulsions and coma preceding death. A not unusual cause of death is the supervention of pneumonia, passing into pulmonary gangrene, a complication favoured, if not actually initiated, by the inhalation of septic material from the ulcerated mouth and gums. Hæmorrhagic pleurisy and pericarditis are also grave complications which sometimes arise.

Diarrhœa and dysentery may complicate scurvy, sometimes perhaps as the result of the scorbutic affection of the mucous membranes; often doubtless superadded to scurvy owing to the subjection to conditions of life favourable to the development of these intestinal disorders.

It is rare, however, in the present day to meet with the worst type of cases, and the readiness with which the disease responds to appropriate treatment renders prognosis far more favourable than it formerly used to be, when it was the scourge of a long sea-voyage, and contributed largely to the mortality of besieged towns. Recovery is all the more complete the earlier treatment is commenced; in other cases there may be left behind permanent evidence of the attack in contraction of limbs and joints by fibrous bands at the site of the intermuscular and subfascial hæmorrhages.

The **diagnosis** of scurvy is not difficult. The possibility of its occurrence in isolated cases in the midst of a well-fed and prosperous community must never be ignored, for in such sporadic cases it will be found sufficiently accounted for by individual peculiarities in respect to diet. The only diseases common to this country with which it is likely to be confounded are purpura and acute leukæmia. In respect to both of these, the diagnosis of the scorbutic nature of the case is greatly assisted by a knowledge of its antecedents. In purpura there is no affection of the gums, although in the severe type (*P. hæmorrhagica*) the hæmorrhagic tendency may be far wider spread than in scurvy. From acute leukæmia, which, as we have seen, may closely simulate scurvy (even etiologically), both as regards its purpuric and its gingival manifestations, the distinction depends mainly upon the result of the examination of the blood.

INFANTILE SCURVY

The recognition of the true nature of so-called "acute rickets" was a distinct gain to clinical medicine, as well as to rational therapeutics. It is, however, to be borne in mind that rickets is not an invariable concomitant of the scurvy which attacks hand-fed

infants between the ages of six and eighteen months. The child exhibits a marked anæmia, which becomes more intense as the disease develops; emaciation is not always present. The infant becomes fretful and restless, and cries when touched or moved, owing to tenderness in the limbs. The most characteristic objective signs are the swellings which make their appearance along the shafts of long bones, especially the femur and tibia. These swellings, which are generally symmetrical, have a pyriform shape, their greatest prominence being opposite to the epiphysial junctions. They are due to hæmorrhage beneath the periosteum, which may be in consequence detached from the bone for a considerable distance. Some crepitation may be felt at the point of junction of the epiphysis with the shaft. The attitude assumed by the child is noteworthy. At first it lies in its cot with the legs flexed on the thighs, but later the limbs lie as if paralysed, flaccid and everted.

Similar hæmorrhages or "hæmatomata" may occur in connection with other bones than those of the lower extremities, *e.g.* the malar bones, ribs, and scapula, and in the upper limbs, at the wrists or the humeral epiphysis. Dr. T. Barlow, to whom medicine is indebted for the most complete clinical and pathological descriptions of the affection (it is known on the continent as "Barlow's disease"), says that a striking feature is an apparent backward depression of the sternum and costal cartilages, as if the ribs were broken.

If the child have any teeth, the gums in their vicinity are swollen and congested, and may be ulcerated. Hæmorrhages may occur elsewhere, *e.g.* beneath the skin, into the cellular tissue of the orbit, causing proptosis first of one eye then of the other; epistaxis, mælæna, hæmaturia, and parenchymatous hæmorrhages in internal organs. There is generally no pyrexia, although the occurrence of a hæmorrhage may be accompanied by a rise of temperature to 101° or 102° .

Under suitable treatment the prognosis is favourable, recovery taking place completely within two or three months.

The **treatment** of scurvy is largely dietetic, consisting in the consumption of fresh food, vegetable and animal. Green vegetables, salads, fruits, especially oranges, lemons, and grapes, and also roots, as carrots, turnips, and potatoes, are all recognised to possess antiscorbutic properties. But the same is true of fresh meat, milk, and eggs. Naturally, in a severe case the conditions do not permit of the free consumption of such articles, but freshly-prepared broths or beef-tea, mashed potatoes, milk and eggs, can almost always be

taken. Where few or none of these are available, lime or lemon juice may be given, and in any case it may be prescribed as an adjuvant to the extent of 3 or 4 ounces daily. For infantile scurvy, the substitution of a diet of artificial foods by one of pure milk, or of mashed potato and milk, with occasional teaspoonfuls of orange or grape juice, will be followed by very satisfactory results. Amongst drugs directly influencing the scorbutic condition, the organic salts of potash, notably the citrate and tartrate, are the chief.

But the various scorbutic lesions may also require attention. Astringent washes for the mouth and gums, such as alum or sulphate of copper, or, if there be much stomatitis and foul breath, the frequent use of gargles of Condyl's fluid or of chlorate of potash.

The hæmorrhages can hardly be restrained by drugs; they will soon be arrested naturally as the condition of the blood improves. To this end iron may be given, either in the form of Blaud's pill or in a mixture with quinine. The bowels must be regulated by mild aperients, such as sulphate of soda, but the use of any strong purgatives is not to be recommended, considering the enfeebled state to which the patient has been reduced. On the other hand, if diarrhœa be present, it should be checked by chalk or bismuth mixtures; 10 grs. of the pulv. cretæ aromaticus c̄ opio, combined with an equal quantity of carbonate of bismuth and taken in milk, being a useful prescription.

Recovery from the state of anæmia and debility may take some time to effect; but under improved diet, with fresh air, bathing, and tonic remedies, it may become quite complete.

PAROXYSMAL HÆMOGLOBINURIA

The circumstances which favour the appearance of hæmoglobin in the urine from destruction of blood corpuscles within the circulation are many and diverse; but there is one affection in which this phenomenon occurs periodically or in paroxysms that has not yet been fully explained pathologically. This is the affection known as paroxysmal hæmoglobinuria, or intermittent hæmatinuria. The determining cause of the attacks is in most cases exposure to cold or chill, and those who are liable to them never seem to get rid of this tendency. In some there is an obvious relationship to Raynaud's disease; in others the antecedent history of malarial taint, added to the periodic nature of the hæmoglobinuric attacks, has led to the inference that the affection is indeed of malarial origin. But there are many cases in which no such antecedents can be proved, and

the evidence is equally strong in favour of syphilis, congenital or acquired, being at the root of the disorder. Lastly, in other cases gout and rheumatism are the only traceable antecedents.

The affection is more common in males than females, and although the period of childhood is not exempt, more cases occur after puberty than before it.

The attack, which follows upon exposure to cold or violent exercise and fatigue, and sometimes after strong emotional disturbance, is ushered in by a sensation of cold, even amounting to rigor, with pallor of the surface, headache, and loss of appetite. Sometimes there is nausea, or actual vomiting, and there may be diarrhoea. The temperature may rise during the attack, but not infrequently it remains normal. Some pain in the limbs and loins may be complained of. The urine passed during the presence of these symptoms is remarkably altered. In quantity it is variable, but in appearance it is totally different from that previously voided. It has a deep red or reddish-brown colour, and contains a notable quantity of albumen. There may be a considerable deposit, which microscopically is found to consist of granular debris. But no (or very few) blood corpuscles can be found in it, although the reaction to guaiacum and ozonic ether is most pronounced, and spectroscopic examination reveals the absorption bands of methæmoglobin, and in some cases (especially later) of oxyhæmoglobin also.

There may be no other symptoms at all, and the whole cycle of the attack will be over in a few hours. Indeed it not infrequently happens that a patient who has been brought to the out-patient room of a hospital in consequence of having passed urine of the character described, has had no recurrence of the attack after his admission into the ward. This does not invariably happen, for sometimes the hæmoglobinuria may be present for a day or two. In susceptible subjects its re-appearance may be brought about by incautious exposure to cold.

It is said that the blood during an attack exhibits evidence of corpuscular destruction and of free hæmoglobin in the serum (hæmoglobinæmia), and that the percentage of hæmoglobin in the blood falls at this time.

There is no definite periodicity in the attacks, sometimes long intervals extending over months or years may occur before a recurrence. But mostly this is liable to take place after a chill.

The condition is readily diagnosed from renal hæmaturia, whilst its paroxysmal character differentiates it from any of the toxic states to which hæmoglobinuria may be due,

It does not appreciably shorten life, therefore the ultimate as well as the immediate prognosis is good.

Not much can be done in the way of *treatment*. It is of prime importance that those liable to the affection should be warmly clad, and avoid every occasion likely to lead to exposure to chills and over-fatigue. During the attack absolute rest in bed, a light milk diet, and warm drinks may be given ; whilst the general condition subsequently is benefited by a course of arsenic and iron. If there be an undoubted malarial or syphilitic predisposition, the medication appropriate to these infections may be prescribed for a time, but it may be doubted whether such treatment is really efficacious either in warding off or in arresting the attacks.

SIDNEY COUPLAND.

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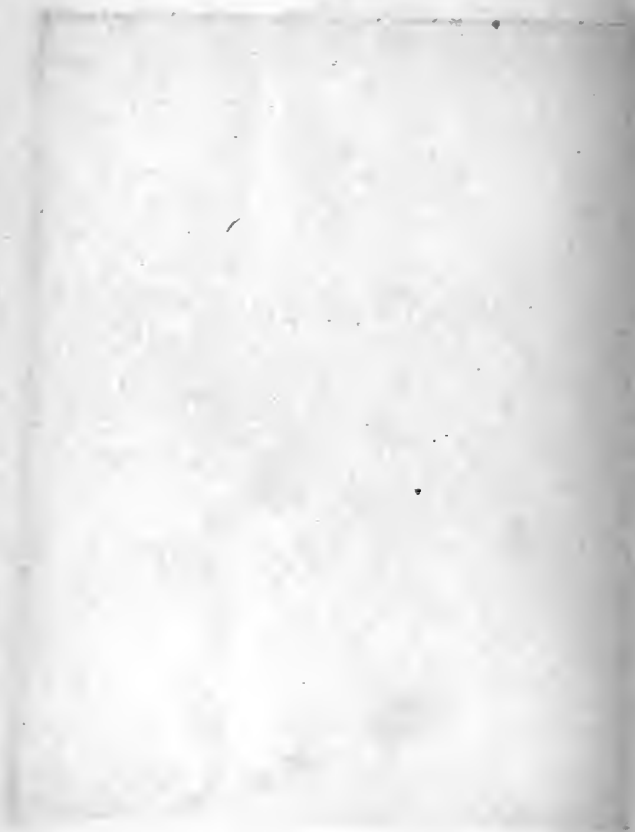
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